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Selective Transformations of Alkylidenecyclobutanes via Ring Opening and Ring Expansion

Yu Teng,[§] Meng-Qiang Cai,[§] and Hong-Shuang Li*

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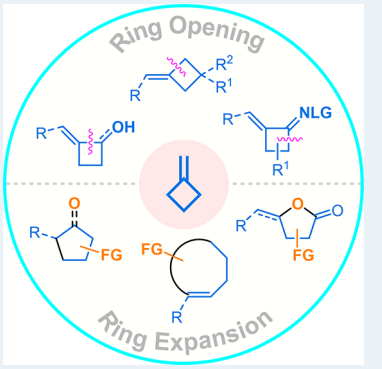
ABSTRACT: Selective activation, cleavage, and controllable reassembly of diverse chemical bonds represent a longstanding pursuit in organic synthesis. Strained carbocycles, featuring broad accessibility, thermodynamic stability, versatility, and intrinsic reactivity, have served as indispensable building blocks for the construction of complicated molecular architectures. In the past few decades, selective transformations of alkylidenecyclobutanes and their derivatives through ring-strain-enabled C−C bond activation have been of particular interest owing to the dual reactivity associated with the exocyclic double bond and the cyclobutane motif. This perspective offers a comprehensive summary of the progress pertaining to the ring-opening and ring-expansion reactions of alkylidenecyclobutanes achieved from 2006 to 2026, with a special focus on transition metal catalysis. Selectivity origins, detailed mechanistic dissection, and emerging opportunities are highlighted to spur new reaction design for strained rings.



KEYWORDS: *alkylidenecyclobutanes, methylidenecyclobutanes, ring opening, ring expansion, transition metal catalysis, selectivity, strain-release*

1. INTRODUCTION

In recent years, small and strained carbocyclic systems, including cyclopropanes, cyclobutanes, alkylidenecyclopropanes (ACPs)/methylidenecyclopropanes (MCPs), and alkylidenecyclobutanes (ACBs)/methylidenecyclobutanes (MCBs) (Figure 1), have garnered substantial interest from synthetic chemists.[1] In terms of strain energy (SE), cyclobutane (26.5 kcal mol^{-1}) is analogous to cyclopropane (27.5 kcal mol^{-1});[2] however, the combination of these cycloalkanes with an exocyclic alkene to form alkylidenecycloalkanes results in significant differences in their intrinsic properties. Accordingly, the SE and olefinic strain (OS) of ACPs (40.9 and 13.4 kcal mol^{-1}, respectively) are much larger than those of ACBs (26.9 and 0.4 kcal mol^{-1}, respectively).[3] Owing to the marked increase in ring strain that imparts high reactivity and selectivity, the ring-opening, ring-expansion, and other miscellaneous functionalizations of ACPs have witnessed rapid growth over the past two decades.[4] By contrast, the selective transformations of ACBs lag far behind.[5] To bridge this reactivity gap, taking advantage of the multifaceted reactivity exhibited by the combination of an electronically activated or unactivated π-system with the cyclobutane σ-system offers new possibilities for strain-release-driven C−C bond activation. Furthermore, the meticulous design of ACBs with diverse substitution patterns and the reliance on external metal catalysts or reagents hold promise for the advancement of novel synthetic methodologies to access a large number of valuable and structurally diverse molecules.

The synthetic approaches to a broad spectrum of ACBs and MCBs from versatile feedstocks have been well-established,[1h,5a] including the most frequently employed Wittig or Horner-Wadsworth-Emmons olefination of preformed four-membered ring systems, ring expansion of cyclopropane compounds, intra- or intermolecular cycloadditions or cyclizations of unsaturated hydrocarbons, as well as other miscellaneous transformations. Consequently, the ready accessibility of these strained carbocycles underpins their enormous potential for numerous synthetic applications. Generally, by leveraging a variety of precious, earth-abundant, and rare-earth metals, the ring-opening modes of ACBs predominantly involve the proximal C−C bond cleavage (Figure 2A, left). Alternatively, incorporating a carbonyl oxygen atom or a hydroxyl group onto the cyclobutane carbon atom adjacent to the alkene also enables the same C−C bond activation, owing to the higher ring strain and reactivity compared to unfunctionalized ACBs. Nevertheless, the regioselective cleavage of the distal C−C bond continues to be a persistent challenge. To date, only one report has successfully demonstrated this unusual ring opening through the introduction of an oxime ester (LG = OBz) into the ACB frameworks under radical-initiated conditions (Figure 2A, right).[6] On the other hand, ring enlargement

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Figure 1. Comparison of the energies of strained carbocycles.

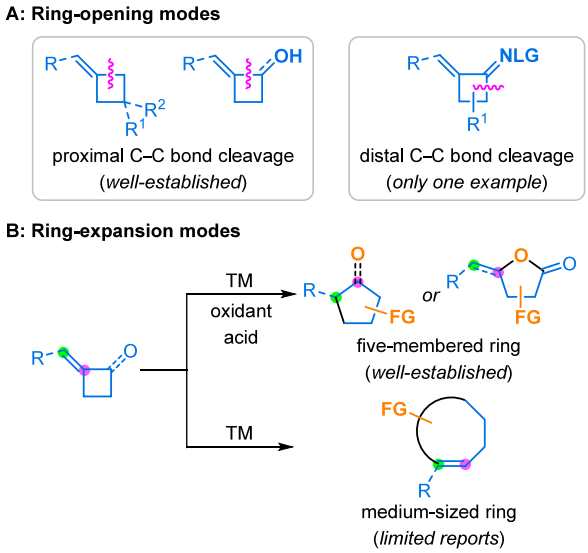

Figure 2. Ring-opening and ring-expansion modes of ACBs. (A) Ring-opening modes. (B) Ring-enlargement modes.

of ACBs and alkylidenecyclobutanones toward either five-membered carbocycles or lactones has been extensively investigated under transition metal catalysis, oxidative, or acidic conditions (Figure 2B, up). In particular, several ACBs tethered with specific functionalities have been employed as alkylmetallic equivalents to facilitate the construction of medium-sized rings (Figure 2B, down), which remain challenging to access through traditional methods. Collectively, these appealing protocols constitute an important component in the development of highly efficient and selective transformations of ACBs.

Since 2020, substantial endeavors from our group have been dedicated to the selective functionalization of a series of strained rings,[7] including ACBs[7a] and ACPs.[7b] Based on these research experiences and inspired by emerging reaction modalities of small ring systems that exhibit distinctive reactivity and selectivity, we have been drawn to the strain-releasing ring-opening and ring-enlargement transformations of ACBs. This perspective summarizes recent advances in the synthetic methodologies of ACBs via selective C−C bond activation over the last two decades, placing an emphasis on transition metal catalysis. On the one hand, a great number of ring-opening reactions of ACBs are systematically outlined. On the other hand, since several ring-enlargement reactions of ACBs have been covered by other reviews in 2014,[5a] 2017,[5b] and 2021,[5c] only representative examples along with the most recent findings are selected and overviewed. It should be noted that selective functionalization of the exocyclic alkenes while retaining the cyclobutane scaffold intact lies beyond the scope of this perspective.[8]

These significant advancements, which primarily harness the ring strain of ACBs as an intrinsic driving force to enable σ-C−C bond activation, are categorized into four sections based on the reaction types of ACBs and their relevant derivatives (e.g., alkylidenecyclobutanones, alkylidenecyclobutanols): (i) ring-opening reactions, (ii) ring opening with concurrent skeletal reorganization, (iii) ring-expansion reactions, and (iv) cascade reactions involving ring expansion. Accordingly, by showcasing a broad spectrum of reaction modalities, providing an in-depth interrogation of the mechanistic pathways, and scrutinizing the advantages and/or limitations, this perspective aims to stimulate novel reaction discoveries of strained carbocycles and to achieve precise control over regio-, chemo-, and enantioselectivity in these reactions.

2. RING-OPENING REACTIONS OF ACBS

Ring-opening reactions of ACBs under transition metal catalysis provide an exquisite and robust avenue for the efficient construction of complicated and valuable linear molecules with new functionalities. Typically, the pathways range from those involving solely the activation of the cyclobutane C−C bond to those depending on the participation of the alkene moiety (Scheme 1). For instance, in the presence of 2-pyridyl as the directing group, site-selective oxidative addition of the $C(sp^2)-C(sp^3)$ bond of ACBs **1.1** to rhodium complexes occurs to generate a five-membered rhodacycle species **1.2**, which may induce subsequent ring-opening, insertion, or skeletal reorganization under harsh reaction conditions.[9] Alternatively, regioselective insertion of the exocyclic alkene into the organometallic species **1.3** would give intermediates **1.4** and **1.5**, which upon β-carbon elimination lead to the ring-opening intermediates **1.6** and **1.7**, respectively. Moreover, in the case of (3-arylcyclobutylidene)acetates **1.8**, the addition of arylrhodium species—generated by transmetalation—across the double bond forms the (cyclobutylmethyl)rhodium intermediate **1.10**. Subsequent β-C elimination generates the ring-opening intermediate **1.11**, which triggers sequential steps involving double 1,4-rhodium migrations to access the skeletal rearrangement product **1.12**.[10] Guided by this mechanistic rationale, transition-metal-catalyzed ring-opening functionalization of ACBs has undergone an upsurge.

Transition-metal-catalyzed C−H activation/annulation of benzamides **2.1** with diverse unsaturated hydrocarbons as C1 synthons has been widely explored.[11] Nevertheless, relevant reactions using ACBs as coupling partners remain significantly underdeveloped. In 2025, Feng et al. reported an elegant Rh^{III}-catalyzed sequential C−H alkenylation and [4+1] annulation with ACBs **2.2** by virtue of the release of ring strain, providing efficient access to 3-methyleneisoindolin-1-ones **2.3** in moderate yields (Scheme 2).[12] *N*-Methoxybenzamides (**2.3a**−**2.3c**) bearing a range of electron-donating and electron-withdrawing groups participated in C−H activation/[4+1] annulation smoothly. In addition, ACB derivatives containing amide (**2.3d**) and alkyl (**2.3e**) substituents also proved to be competent substrates. Moreover, this strain-release-enabled protocol holds great potential for downstream diversification of pharmaceutically relevant molecules, as demonstrated for compound **2.3f**. Control experiments indicated the formation of a C−H alkenylation product as a key intermediate, while a deuterium labeling experiment suggested the involvement of a Rh−H species in the migration process. Based on these experimental observations, the authors proposed that the mechanism begins with C−H activation by the in situ-generated catalyst

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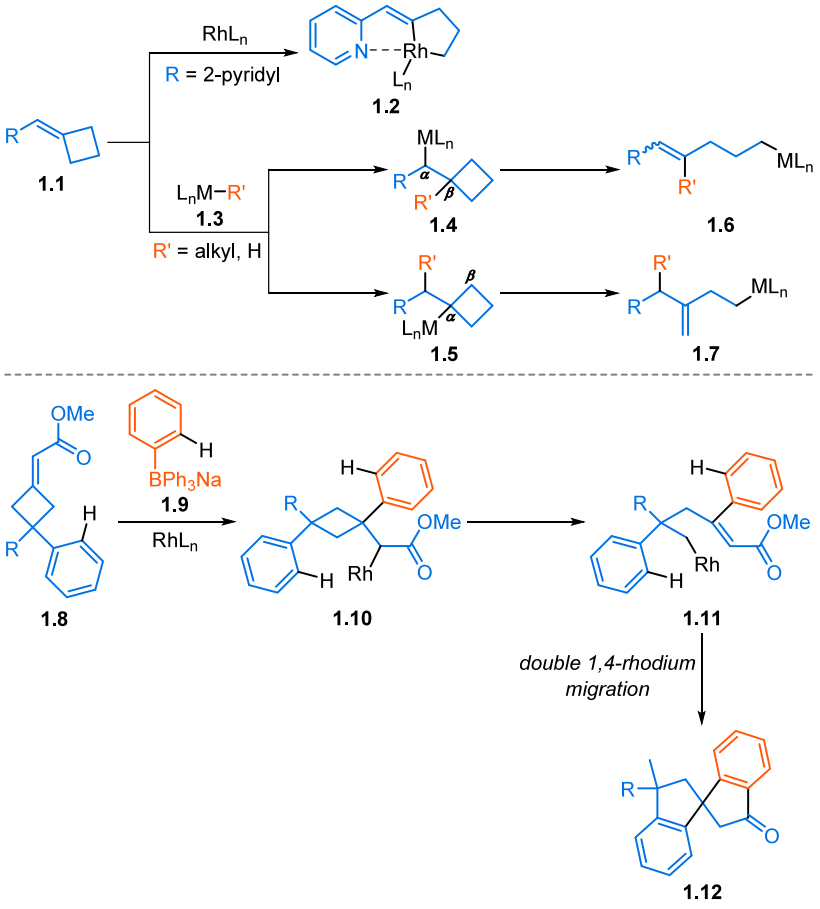
Scheme 1. Transition-Metal-Catalyzed Ring Opening of ACBs



(Cp^*RhX_2) to form a five-membered rhodacycle intermediate **2.4**. Following alkene coordination, the resulting complex **2.5** undergoes regioselective migratory insertion to give a seven-membered intermediate **2.6**, which upon β-H elimination affords intermediate **2.7**. Ensuing reductive elimination produces the C−H alkenylation product **2.8** along with a Rh^I catalyst. Oxidative addition of the N−O bond of **2.8** onto Rh^I, followed by intramolecular migratory insertion and a second β-H elimination, leads to complex **2.11**. Further migratory insertion with subsequent β-C elimination generates the linear Rh^{III}−alkyl species **2.13**, thus completing the migration process. Final protonation releases the 3-methyleneisoindolin-1-one product **2.3** with concurrent regeneration of the Rh^{III} catalyst. This unprecedented ring-opening study extends the applicability of strained ring systems in site-selective transformations.

The efficient and highly selective hydrofunctionalization of unsaturated hydrocarbons, particularly those encompassing strained rings, has become a frontier area of research in synthetic chemistry. Despite this progress, studies on the ring-opening hydrofunctionalization of ACBs face significant challenges in controlling regio-, chemo-, and stereoselectivity. In 2024, in an effort to perform hydrosilylation of diverse alkenes, Dong et al. found that catalytic amounts of rare-earth metal ($La(HMDS)_3$) promoted regioselective ring-opening dihydrosilylation of (cyclobutylidenemethyl)benzene **3.2** with excess $PhSiH_3$ **3.1**, leading to adduct **3.3** in 66% yield (Scheme 3).[13] However, this work reported only one example of ring-opening dihydrofunctionalization, and a detailed mechanism was not presented.

Transition-metal-catalyzed/mediated asymmetric ring-opening coupling of arylidenecyclobutanes remains an uncharted area. This is presumably due to the relatively small strain release (2.7 kcal mol^{-1}) from MCB to cyclobutane,[14] which renders the migratory insertion of the trisubstituted alkene moiety of arylidenecyclobutanes into metal−hydride species challenging. To overcome this obstacle, in 2025, relying on the Cu^I/(*S*,*S*)-Ph-BPE catalytic system, the group of Ge and Lu achieved a rare example of ring-opening dihydroboration reactions of arylidenecyclobutanes **4.2** with HBpin **4.1** to provide a number of enantioenriched 1,5-diboronate products **4.3** (Scheme 4).[15] The observed ring-opening activity and enantioselectivity may originate from the small steric repulsion and electron-rich nature of (*S*,*S*)-Ph-BPE, whereas the combination of CuOAc with (*S*)-DTBM-Segphos only promoted asymmetric ring-retaining monohydroboration, affording enantioenriched α-cyclobutyl benzylboronates. Arylidenecyclobutanes with both electron-rich (**4.3a**−**4.3c**) and electron-poor (**4.3d** and **4.3e**) aryl and heteroaryl (**4.3f**) groups were uniformly amenable to this completely atom-economical dihydroboration, and the anticipated chiral 1,5-diboronate compounds were isolated in moderate to good yields with high enantioselectivity. Control experiments revealed that the ring-opening of arylidenecyclobutanes via β-C elimination proceeds considerably slower than that of arylidenecyclopropanes. Moreover, the

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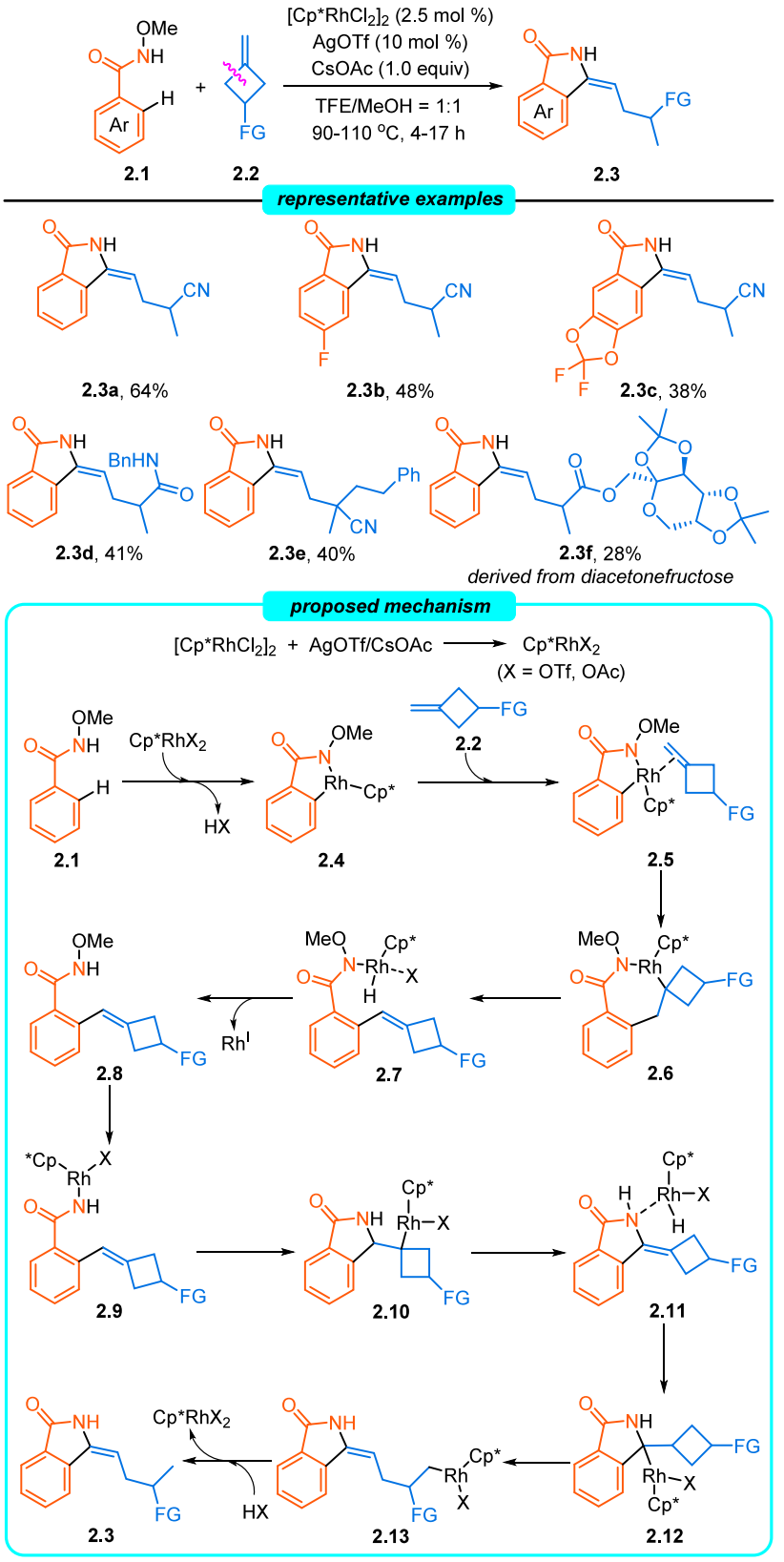
Scheme 2. Rh-Catalyzed C−H Alkenylation/[4+1] Annulation of Benzamides with ACBs



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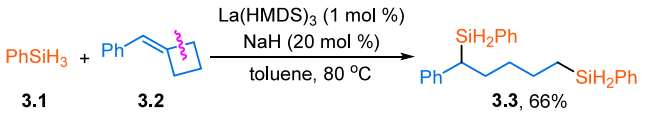
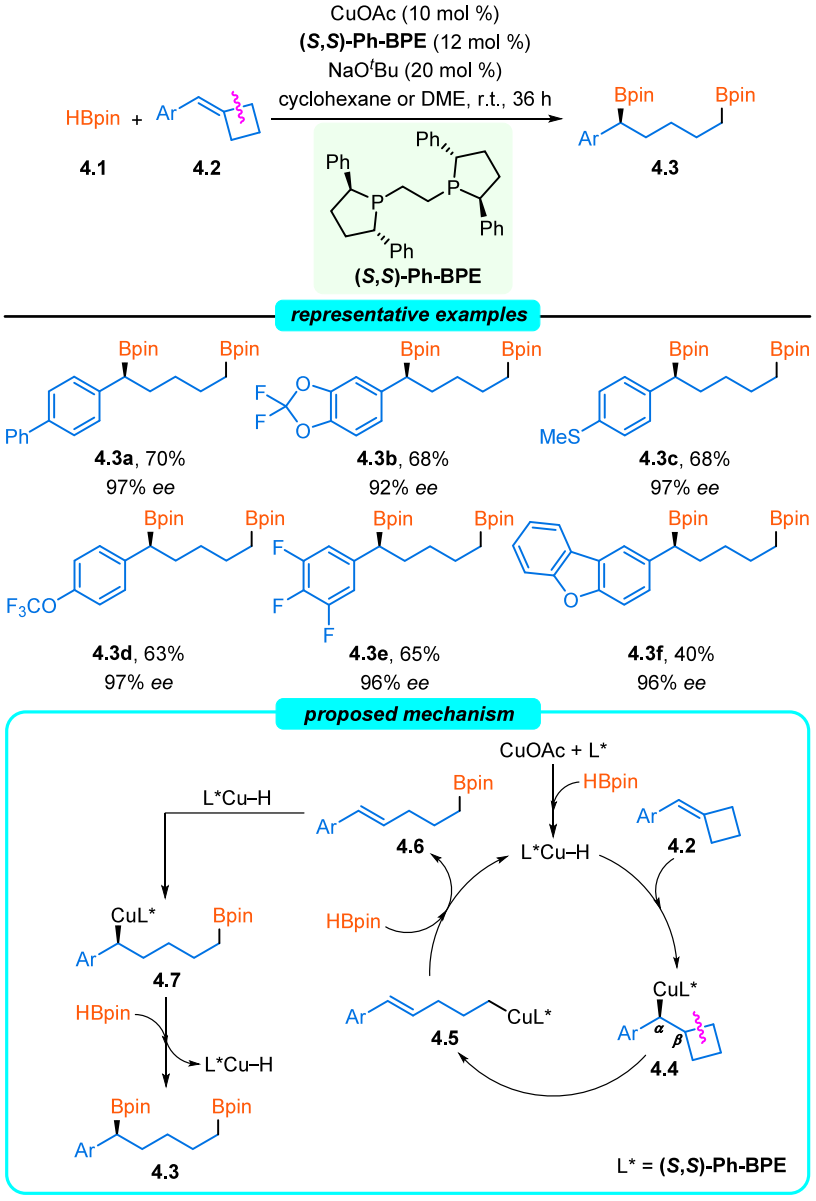
Scheme 3. La-Catalyzed Regioselective Ring-Opening Dihydrosilylation of a Benzylidenecyclobutane



authors identified the ring-opening alkenylboronate **4.6** as a reactive intermediate in the coupling of arylidenecyclobutane **4.2** with 1.3 equiv of HBpin **4.1** under standard reaction conditions. Based on these findings, a plausible catalytic mechanism for the ring-opening dihydroboration was proposed. Initially, migratory insertion of arylidenecyclobutane **4.2** into the reactive copper−hydride intermediate, formed by the reaction of the copper catalyst and the chiral ligand with HBpin, provides benzylcuprate intermediate **4.4**. Subsequent β-C elimination occurs to give a ring-opening alkenylcuprate species **4.5**, which undergoes σ-bond metathesis with HBpin, leading to the key (*E*)-alkenylboronate intermediate **4.6**. Stereoselective migratory insertion of the internal alkene into the Cu−H species yields borylalkylcuprate **4.7**, which couples with HBpin through σ-bond metathesis to release the target product **4.3** with concurrent regeneration of the active Cu−H catalyst. Consequently, this work not only provides a practical and straightforward approach for the enantioselective transformation of ACBs but also emphasizes the significance of earth-abundant metal catalysis.

The dual reactivity exhibited by the exocyclic alkene and strained cyclobutane motifs of MCBs allows versatile and selective functionalization via strain-driven C−C bond cleavage, thus considerably expanding the chemical diversity of these unsaturated systems. During the preparation of this review, an impressive Ni^0-catalyzed ring-opening 1,4-dicarbofunctionalization of MCBs **5.2** with aryl triflates **5.1** and benzylmagnesium chlorides

Scheme 4. Cu-Catalyzed Enantioselective Ring-Opening Dihydroboration of ACBs



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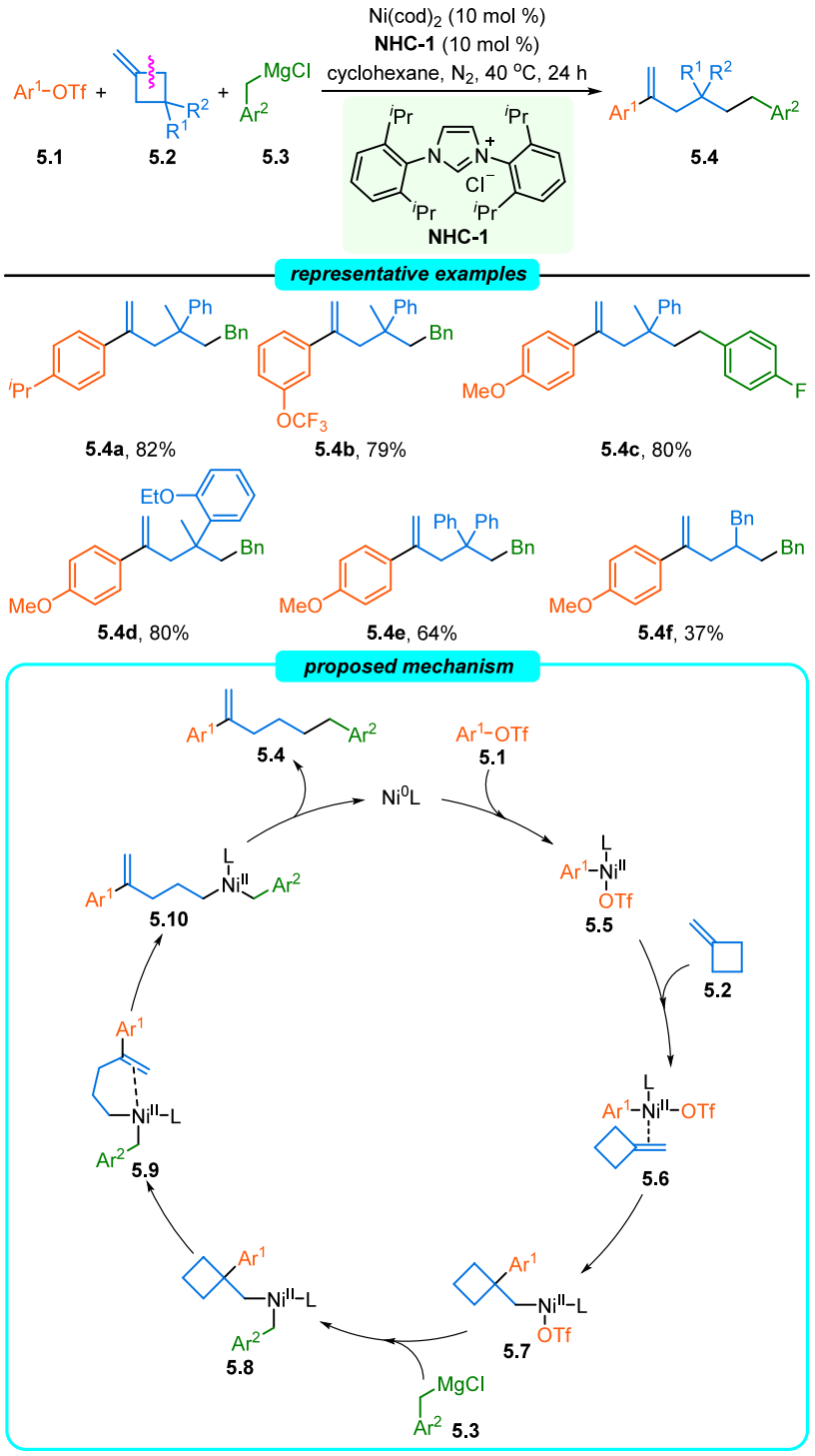
Scheme 5. Ni-Catalyzed Ring-Opening 1,4-Dicarbofunctionalization of MCBs



5.3 via the same strain-release-enabled C−C activation was reported by Wang et al., thus providing regioselective access to valuable molecules **5.4** with noncontiguous C(sp^3) and C(sp^2) centers under mild conditions (Scheme 5).[16] The key to the success of the multicomponent protocol lies in the use of the nitrogen-heterocyclic carbene (NHC) catalyst that possesses appropriate electronic and steric properties; as a result, a great number of MCBs containing quaternary carbon centers (**5.4a**−**5.4e**) were well-tolerated. However, due to the competitive β-H elimination, the MCB with a tertiary carbon center afforded the desired 1,4-dicarbofunctionalization product **5.4f** in only 37% yield. On the basis of a series of mechanistic studies in conjunction with density functional theory (DFT) calculations, the authors proposed a plausible reaction pathway that starts with the coordination of Ar^1OTf **5.1** to the active Ni^0−NHC species, followed by irreversible oxidative addition. Subsequent olefin coordination to the resulting **5.5** gives four-coordinate Ni−MCB complexes **5.6**, which undergoes a

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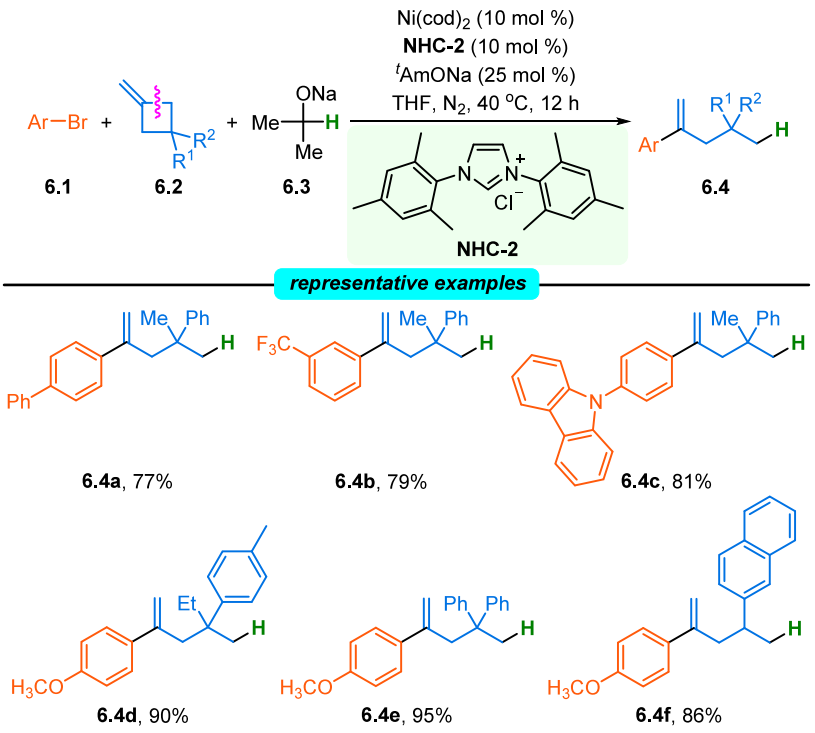
Scheme 6. Ni-Catalyzed Ring-Opening 1,4-Hydrocarbofunctionalization of MCBs



rate-determining 1,2-insertion step to form an alkyl−Ni^{II} intermediate **5.7**. Following transmetalation with the Grignard reagent **5.3**, β-C elimination of the corresponding alkyl−Ni^{II}−benzyl species **5.8** proceeds through C−C σ-bond cleavage to produce intermediate **5.9**. Isomerization, followed by reductive elimination, furnishes the ring-opening product **5.4** and regenerates the active Ni^0−NHC catalyst to initiate the next cycle. Additionally, an alternative mechanism, which involves β-C elimination of **5.7** ahead of transmetalation, was postulated. Subsequent isomerization and reductive elimination delivered the product **5.4**. In view of the substantially low activation barriers following intermediate **5.7** compared to the 1,2-insertion step, both pathways may proceed in parallel.

Meanwhile, the ring-opening 1,4-hydrocarbofunctionalization of MCBs **6.2** with aryl bromides **6.1** was also accomplished by the same group using sodium isopropoxide **6.3** as the hydrogen source under the synergistic catalysis of Ni^0 and another analogous NHC catalyst (Scheme 6).[16] In this case, sodium *tert*-pentoxide (^{t}AmONa) served as the base dictating the β-C elimination process. Notably, the Ni^0 catalytic system proved applicable to a variety of aryl and heteroaryl bromides as well as to MCBs bearing quaternary and tertiary carbon centers, allowing the preparation of terminal alkenes **6.4** in good to excellent yields. Isotope-labeling studies in combination with the kinetic isotope effect (KIE = 3) unequivocally demonstrated that hydride transfer is involved in the turnover-limiting step. Despite these novel ring-opening patterns and the appealing versatility in the design of molecular diversity and complexity, the substrate classes remain narrowly defined, leaving ample chemical space for methodological advancement.

The relatively low reactivity of ACBs typically left the cyclobutane structure intact.[8] To increase both ring strain and reactivity, chemists turned their attention to the conversion of a proximal sp^3 carbon into either an sp^2-hybridized ketonic carbon[17] or a carbon bearing a hydroxyl group.[18] This strategy led to the advancement of various highly reactive ACBs, such as alkylidenecyclobutanones and alkylidenecyclobutanols, thereby offering more opportunities in site-selective transformations involving ring cleavage.

Although (*Z*)-alkenes are valuable structural units in natural products,[19] to date, their synthesis still poses a significant challenge due to the thermodynamic instability compared to (*E*)-alkenes. In 2016, the Song group unveiled a Pd^0-catalyzed ring-opening coupling of 2-alkylidenecyclobutanones **7.2** with arylboronic acids **7.1** via C−C bond activation, providing a direct and efficient synthesis of 1,5-diphenylpent-4-en-1-ones **7.3** with excellent *Z*-selectivity.[20] The introduction of a carbonyl group into the cyclobutane framework was demonstrated to facilitate the $C(sp^2)$−$C(sp^2)$ bond cleavage of 2-alkylidenecyclobutanones. As shown in Scheme 7, this protocol was compatible with both coupling partners bearing diverse functional groups, thus affording good to excellent yields of (*Z*)-γ,δ-unsaturated ketones. Deuterium experiments and GC−MS analysis suggested the involvement of 1,2-addition of an arylpalladium species **7.4** to the 2-alkylidenecyclobutanone **7.2** to release the ring strain, and ruled out insertion of the $C(sp^2)$−$C(sp^2)$ bond of 2-alkylidenecyclobutanone into Pd^0. The resulting Pd^{II} cyclobutanolate intermediate **7.5** then undergoes selective β-C elimination via $C(sp^3)$−$C(sp^2)$ bond cleavage, leading to the vinylpalladium species **7.6** (pathway a). By contrast, the alkylpalladium species **7.6′**, which would arise from β-C elimination via $C(sp^3)$−$C(sp^3)$ bond cleavage (pathway b), was not observed. Protonolysis, followed by transmetalation with boronic acids **7.1**, delivers the desired

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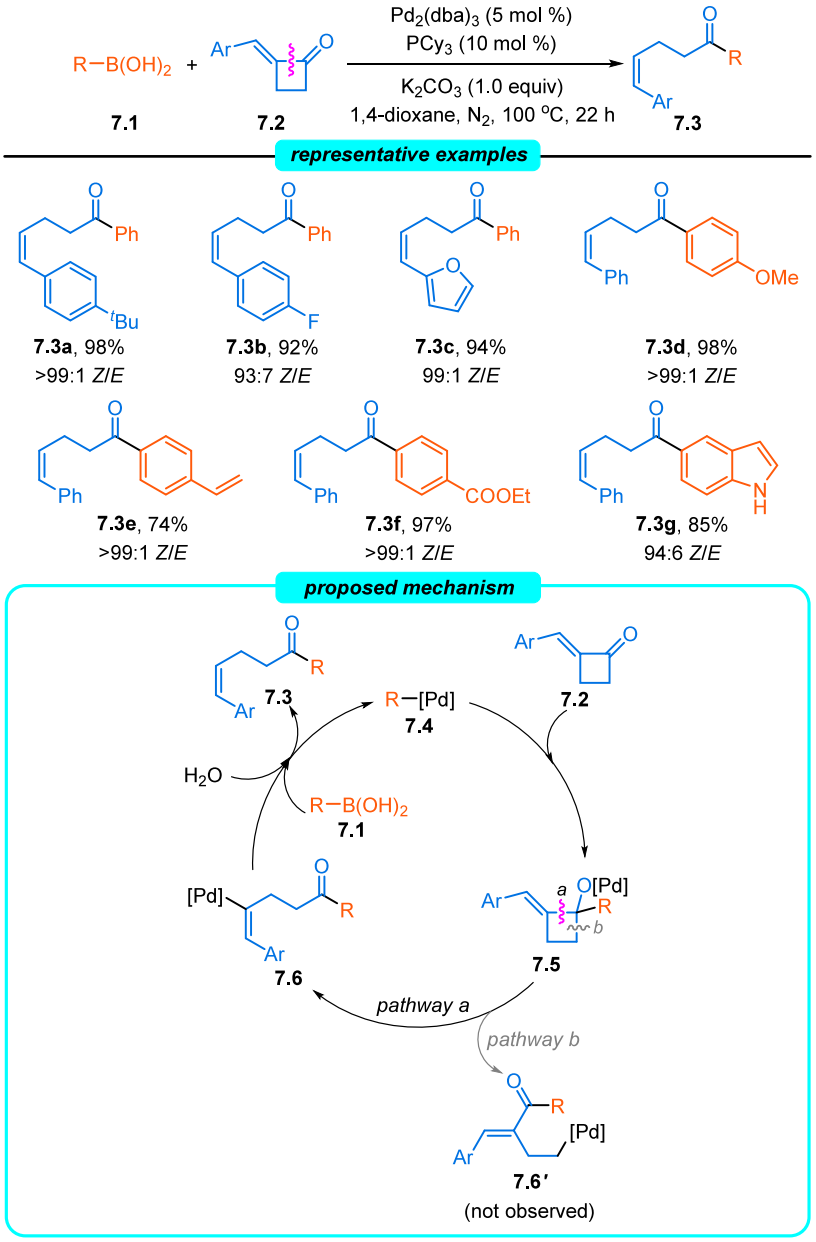
Scheme 7. Pd-Catalyzed Ring-Opening Coupling of 2-Alkylidenecyclobutanones with Arylboronic Acids



(*Z*)-alkene **7.3** with concomitant reproduction of the arylpalladium species **7.4**. Note that the 1,2-addition is favored over the 1,4-addition due to the exocyclic double bond and the ring strain imparted by the carbonyl group, and that *Z*-selectivity likely stems from the *E* configuration of the 2-alkylidenecyclobutanone component. This seminal study offers an elegant and powerful alternative to the synthesis of (*Z*)-alkenes, rendering them particularly appealing for downstream modification.

On the other hand, unsaturated ketones are fundamental scaffolds ubiquitously found in pharmaceuticals and naturally occurring products. However, general synthetic approaches to γ,δ-unsaturated ketones remain limited. To address this gap, a Pd^0-catalyzed stereoselective ring-opening coupling of 2-alkylidenecyclobutanols **8.2** with organic halides **8.1** by means of a strain-release-driven strategy was accomplished by Cao, Xu, and co-workers (Scheme 8).[18] A variety of functional groups on the substrates, including aryl, heteroaryl, alkyl, alkenyl, benzyl, and alkynyl, were successfully incorporated into the γ,δ-unsaturated carbonyl compounds **8.3**. Especially noteworthy is the forge of a trisubstituted C−C double bond under mild reaction conditions. As depicted in the proposed mechanism, oxidative addition of halide **8.1** to the Pd^0−phosphine complex generates a Pd^{II} species **8.4**. Subsequent ligand exchange between 2-alkylidenecyclobutanol **8.2** and **8.4** in the presence of the Ag^I salt gives rise to a palladium alkoxide **8.5**, which undergoes selective β-C elimination to provide the ring-opening intermediate **8.6**. This $C(sp^3)$−$C(sp^2)$ bond cleavage is considered as the key step. Finally, reductive elimination yields the γ,δ-unsaturated ketone **8.3**, along with regeneration of the Pd^0 catalyst. The complementary stereochemical outcomes

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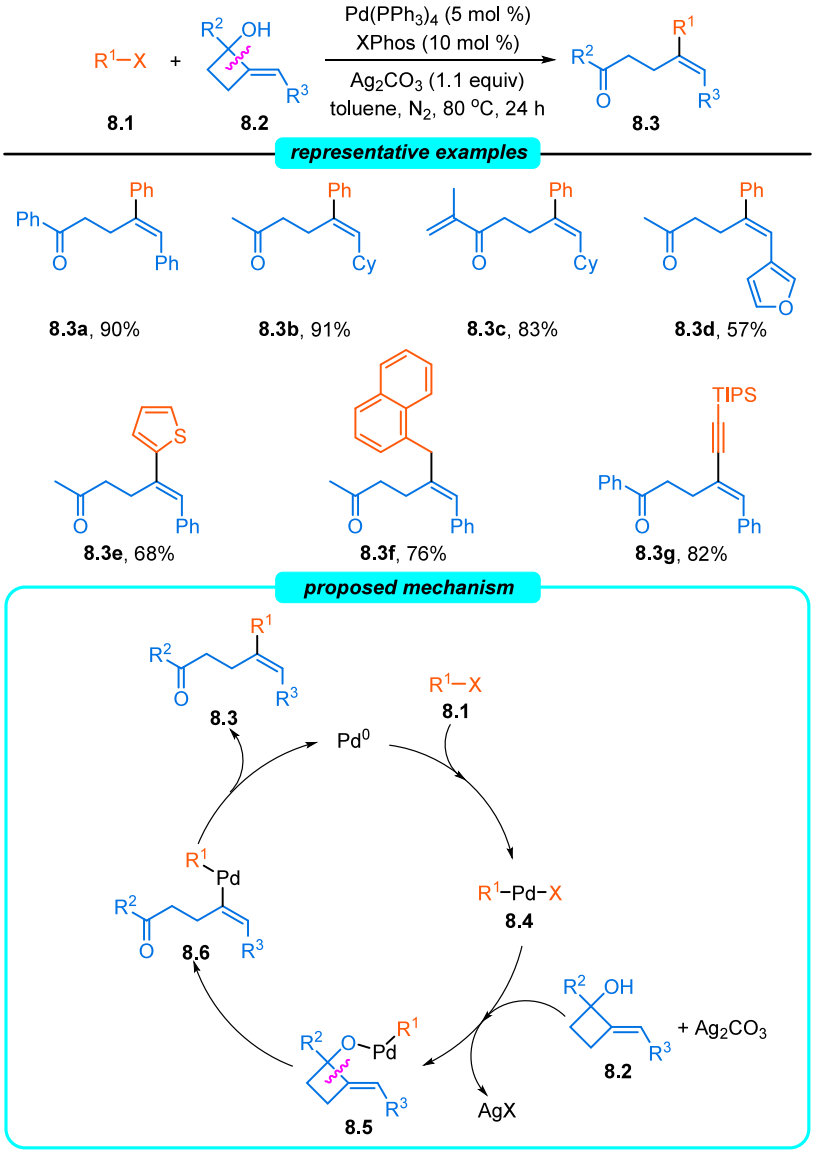
Scheme 8. Pd-Catalyzed Ring-Opening of 2-Alkylidenecyclobutanols with Halides



significantly expand the synthetic toolbox for accessing diverse, privileged unsaturated ketones.

Compared with transition metal catalysis, electrochemical synthesis offers several significant advantages, including the avoidance of external oxidants/reductants, energy efficiency, and high selectivity, thereby aligning with the principles of green chemistry and sustainable development. In 2026, He, Zhang, and co-workers realized the first electrochemical ring-opening functionalization of 2-alkylidenecyclobutanols **9.2** with sulfonyl radical and halogen radical sources for the preparation of pharmaceutically valuable γ,δ-unsaturated carbonyl compounds (Scheme 9).[21] Distinct from the aforementioned activation mode targeting the hydroxyl functionality,[18] this method proceeded via radical-initiated selective addition to the alkene followed by the release of the ring strain. Wide functional group tolerance was observed as demonstrated by the formation of the γ-sulfonylated and γ-halogenated products (**9.3a**−**9.3f**), albeit with poor stereoselectivity for the ring-opening chlorination. Surprisingly, a cyclopropane product **9.3 g** was obtained when a cyclohexyl group was introduced instead of aryl groups. Control experiments indicated two distinct reaction pathways governing the ring-opening sulfonylation/chlorination and bromination processes, respectively. The sulfonyl or Cl radical, formed by oxidation of the sulfonyl hydrazide or chloride at the anode, undergoes regioselective addition to the exocyclic double bond to generate benzylic radical intermediate **9.4**. Subsequent strain-release-driven homolytic C−C bond cleavage yields radical **9.5**, which is further oxidized at the anode to produce a cation species **9.6**. Final deprotonation delivers γ-sulfonylated and γ-chlorinated unsaturated ketones. Moreover, direct anodic oxidation of **9.4** followed by ring opening of the resulting benzyl cation **9.7** cannot be ruled out. In sharp contrast, in the presence of $^{n}Bu_4NBr$, anodic oxidation of bromide anion leads to a Br^+ cation, which adds to the double bond to provide bromonium ion **9.8**. The ensuing process depends on the nature of the R^1 substituent. For an aryl-substituted substrate, a more stable benzyl cation intermediate **9.7** is preferentially formed via deprotonation

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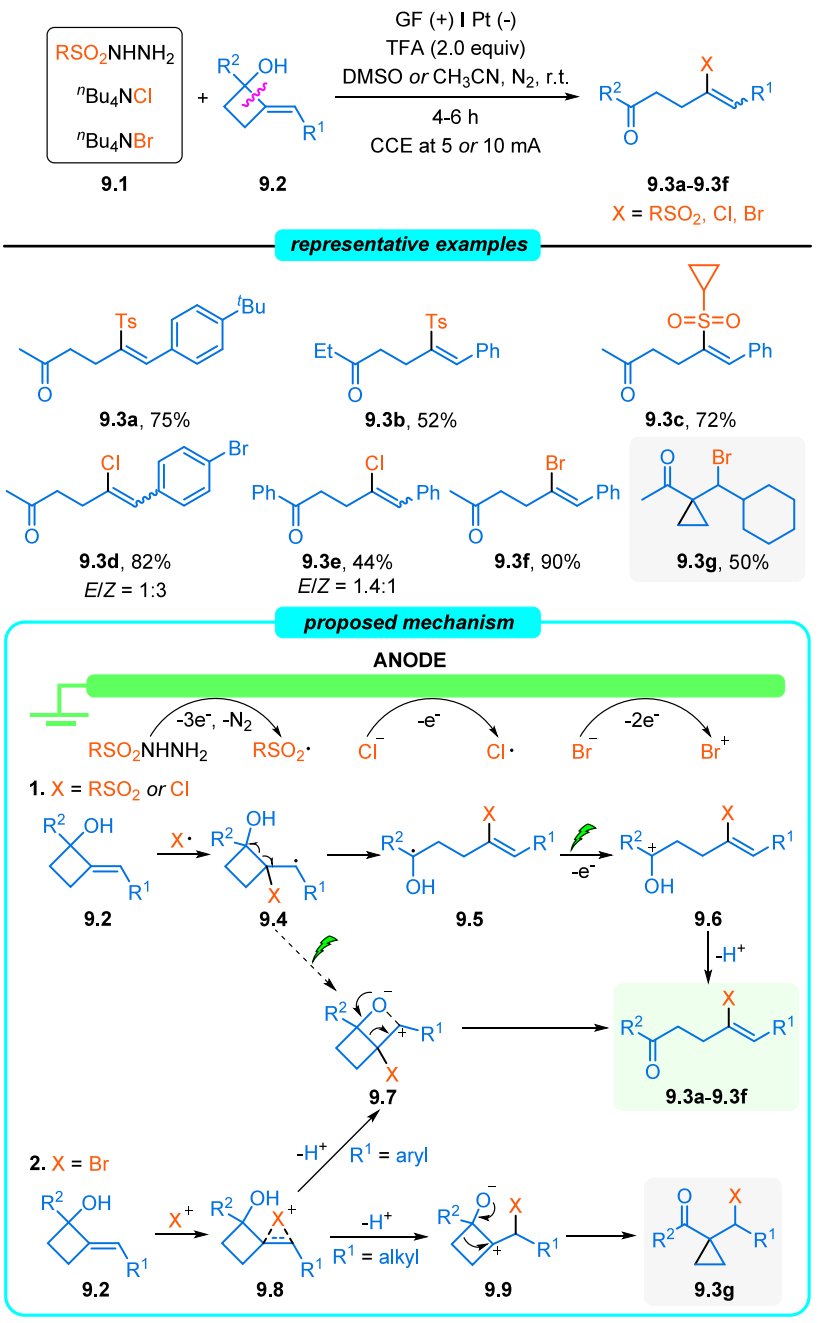
Scheme 9. Electrochemical Ring-Opening Functionalization of 2-Alkylidenecyclobutanols



of **9.8**, which then furnishes the product. Alternatively, in the case of an alkyl-substituted substrate, electrophilic bromination leads to a more stable tertiary carbocation **9.9**, which upon 1,2-alkyl migration affords the cyclopropane product **9.3 g**. This protocol paves the way for the electrochemical radical-initiated selective functionalization of ACBs and their surrogates.

Similar to electrochemistry, photoredox catalysis also enables the activation of diverse substrates by means of external energy input to generate active radical species, thus significantly expanding the chemical space with novel synthetic paradigms implemented. Although photocatalytic ring-opening transformations of 2-alkylidenecyclobutanols allow selective cleavage of $C(sp^2)-C(sp^3)$ bonds and forge new carbon−carbon and carbon−heteroatom bonds under mild conditions, only a few examples have been reported to date. Specifically, the Ackermann group in 2023[22] and the Wang group in 2026[23] independently achieved radical-induced ring-opening functionalization of 2-alkylidenecyclobutanols (**10.2a** and **10.2b**) using sulfonyl chloride (**10.1**), *N*-fluorosulfamoylpyridinium salt (**10.4**), and bromomethylsulfonyl fluoride (**10.5**) as the radical precursors (Scheme 10). These photocatalytic protocols underscore their potential in the construction of C−S, C−N, or C−C bonds with excellent regioselectivity

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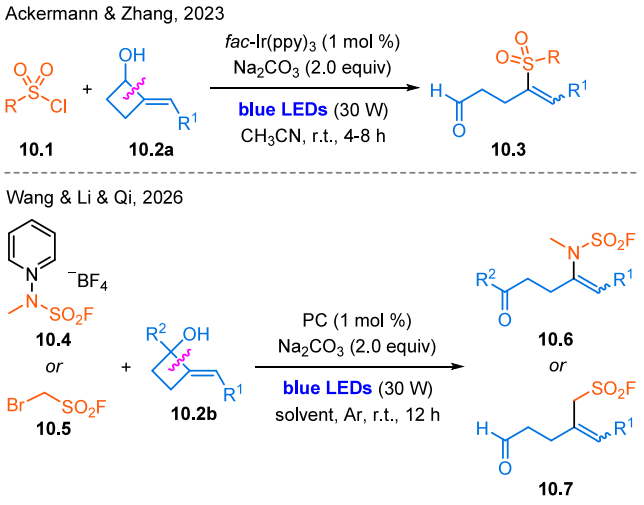
Scheme 10. Photocatalytic Ring-Opening Functionalization of 2-Alkylidenecyclobutanols



across a broad range of 2-alkylidenecyclobutanol substrates, thereby providing a conceptually distinct alternative to conventional approaches toward γ,δ-unsaturated carbonyl compounds.

3. RING OPENING OF ACBS WITH CONCURRENT SKELETAL REORGANIZATION

It is well-known that the regioselective ring-opening reactions of ACBs often lead to a series of linear compounds with diverse functional groups. In the past decade, an increasing number of organic chemists have embarked on systematic investigations into the ring-opening reactions of ACBs with concomitant skeletal reassembly of other functionalities in either an intermolecular or intramolecular manner. Typically, these approaches enable a variety of unexpected annulative transformations, allowing rapid and atom-economical construction of a myriad of bicyclic or polycyclic compounds. This section focuses on transition metal catalysis involving various mechanistically distinct pathways, and also covers late-transition metals such as the highly toxic thallium (Tl) salts.

Selective C−C bond activation of unsaturated hydrocarbons, especially MCBs, has evolved into one of the most fascinating research topics in the field of organometallic chemistry. In 2021, building on their earlier work on the ring-opening of 2-alkylidenecyclobutanols,[18] Cao, Xu, and colleagues developed a Pd^0-catalyzed sequential C−C bond activation of MCBs **11.1** and Suzuki cross-coupling with aryl and alkenyl boronic acids **11.2** (Scheme 11).[24] They demonstrated that a novel phosphoramidite ligand containing two bulky silicon-based substituents was crucial for enabling the transformation. This tandem reaction provided expedient access to a diverse range of multisubstituted indanes **11.3** in good to excellent yields, featuring broad substrate scope with respect to both the boronic acids (**11.3a**−**11.3c**) and MCBs (**11.3d**−**11.3f**). A gram-scale reaction and functional group derivatization further underscored the practical utility of this approach. The plausible mechanism proposes that oxidative addition of the Pd^0 catalyst to the C−Br bond of **11.1** generates an arylpalladium intermediate **11.4**, which undergoes regioselective migratory insertion to yield a σ-alkylpalladium species **11.5**. Subsequent β-carbon elimination driven by the release of ring strain affords an alkylpalladium intermediate **11.6**. Finally, Suzuki cross-coupling with boronic acid **11.2**, followed by reductive elimination, delivers the desired indane **11.3**.

Alkylidenecyclobutanones are more prone to ring opening with simultaneous skeletal reorganization due to the replacement of the sp^3-hybridized carbon of ACBs by an sp^2-hybridized carbonyl carbon. In 2015, Xia, Wu, and co-workers achieved a palladium-catalyzed tandem annulation of 2-(2-bromobenzylidene)cyclobutanones **12.1** with 2-alkynylphenols **12.2**, offering an effective approach for accessing a vast array of natural product-like benzo[*b*]naphtho[2,3-*d*]-oxocin-6-ones **12.3** (Scheme 12).[25] It is worth noting that both components, bearing either an electron-donating group (e.g., a trimethylsilyl group in **12.3d**) or an electron-withdrawing group, participated efficiently in the tandem cyclization reaction. In the proposed mechanism, oxidative addition of 2-(2-bromobenzylidene)cyclobutanone **12.1** to Pd^0 generated in situ would initially form a Pd^{II} species **12.4**. Following coordination to the triple bond of 2-alkynylphenol **12.2**, insertion of the triple bond into the Pd−C bond of **12.4** occurs to generate a vinyl−Pd^{II} species **12.5**, which then undergoes intramolecular insertion into the double bond to give intermediate **12.6**. Selective β-C elimination produces the ring-opening acyl−Pd^{II} species **12.7**. Finally, an intramolecular nucleophilic attack in the presence of KOAc furnishes the desired fused polycycle **12.3** and regenerates the Pd^0 catalyst. By capitalizing on the ring opening of alkylidenecyclobutanones via C−C bond activation, this tandem process enables the simultaneous assembly of three bonds (two C−C bonds and one C−O bond), thus representing a novel strategy for constructing elaborate molecular architectures.

In the same year, the same group disclosed a silver-catalyzed three-component reaction system composed of *N*′-(2-alkynylbenzylidene)hydrazides **13.1**, 2-alkylidenecyclobutanones **13.2**, and H_2O, which enabled the construction of 3-(pyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acids **13.3** in moderate to good yields through sequential 6-*endo*-dig cyclization, [3+2] cycloaddition, and rearrangement (Scheme 13).[26] In this transformation, the influence of 2,6-dimethylpyridine as the base on the reaction outcome was critical. Furthermore, excellent compatibility with diverse functional groups was demonstrated for the one-pot preparation of fused heterocycles, with aryl, heteroaryl, and alkyl groups all being well-tolerated. The reaction mechanism involves an intramolecular 6-*endo*-dig cyclization of *N*′-(2-alkynylbenzylidene)hydrazide **13.1** under silver catalysis to give an isoquinolinium-2-yl amide **13.4** as the key intermediate, which then undergoes subsequent [3+2] cycloaddition with 2-alkylidenecyclobutanone **13.2**. Elimination of the tosyl group from the resulting intermediate **13.5**, followed by deprotonation, produces intermediate **13.8**. Ensuing nucleophilic attack of H_2O on the carbonyl group in the presence of the base would induce the C−C bond cleavage. Final aromatization in air leads to the formation of 3-(pyrazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid **13.3**. The feasibility of these tandem reactions between 2-alkylidenecyclobutanones and in situ-generated *N*-imide ylides opens new avenues for incorporating nitrogen atoms into value-added molecules.

2-((*E*)-Benzylidene)cyclobutan-1-one oxime esters, as a unique class of ACB derivatives, exhibit high reactivity toward ring-opening functionalization due to the low dissociation energy of the N−O bond. In 2023, Liu, Zhang, and co-workers disclosed a Cu^{II}-mediated radical-initiated

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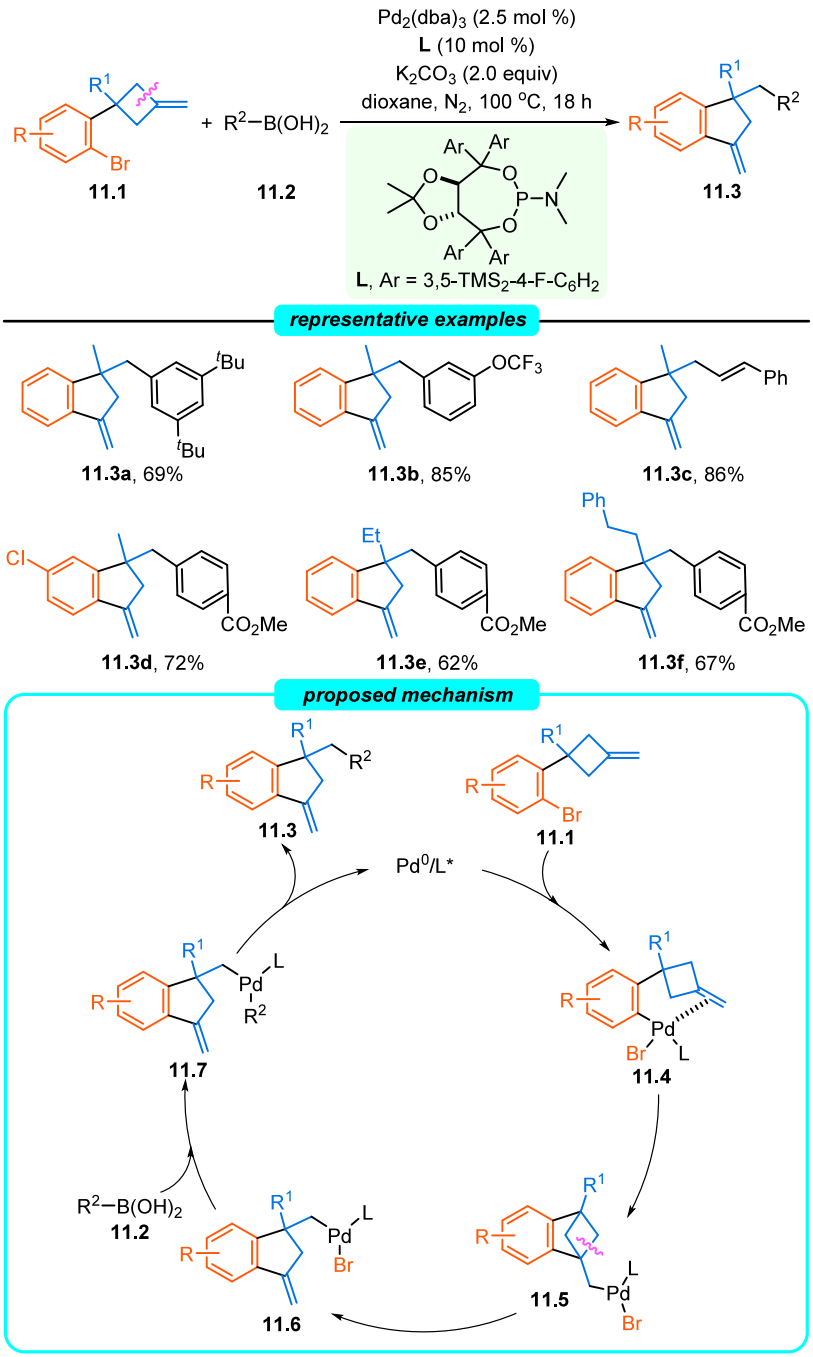
Scheme 11. Pd-Catalyzed C−C Bond Activation/Suzuki Coupling of MCBs



ring-opening relay cascade carboannulation of [60]fullerene **14.1** with 2-((*E*)-benzylidene)cyclobutan-1-one oxime esters **14.2** for the highly selective synthesis of novel Cl-/Br-incorporated [60]fullerene-fused cyclopentanes (**14.3**) under simple redox-neutral conditions (Scheme 14).[6] In this transformation, low-cost copper salts, which are essential for the N−O bond cleavage, served as both promoters and halogen sources. Notably, oxime esters bearing electron-rich (**14.3a**) and electron-poor groups (**14.3b**) on the benzene ring, as well as those with a 2-furanyl group (**14.3c**), were well-tolerated. Furthermore, the alkyl and phenyl groups (**14.3d**−**14.3f**) at different positions of the cyclobutanone rings had negligible impact on the relay cascade transformation. Based on control experiments, a tentative mechanism involving a selective C−C bond cleavage/radical cycloaddition/halogen atom incorporation cascade was proposed. Specifically, single-electron transfer (SET) from Cu^{n+} to the N−O bond of oxime ester **14.2** forms an iminyl radical **14.4** with concomitant release of a $Cu^{(n+1)+}$ species. Ensuing β-scission of the C−C bond occurs to yield a distal radical **14.5**, which adds to [60]fullerene **14.1** to provide a fullerenyl radical **14.6**. Intramolecular cyclization of **14.6** gives a benzyl radical **14.7**, which undergoes further oxidation by the in situ-generated $Cu^{(n+1)+}$ to form a benzyl cation **14.8**. Final nucleophilic addition of X^- furnishes [60]fullerene-fused

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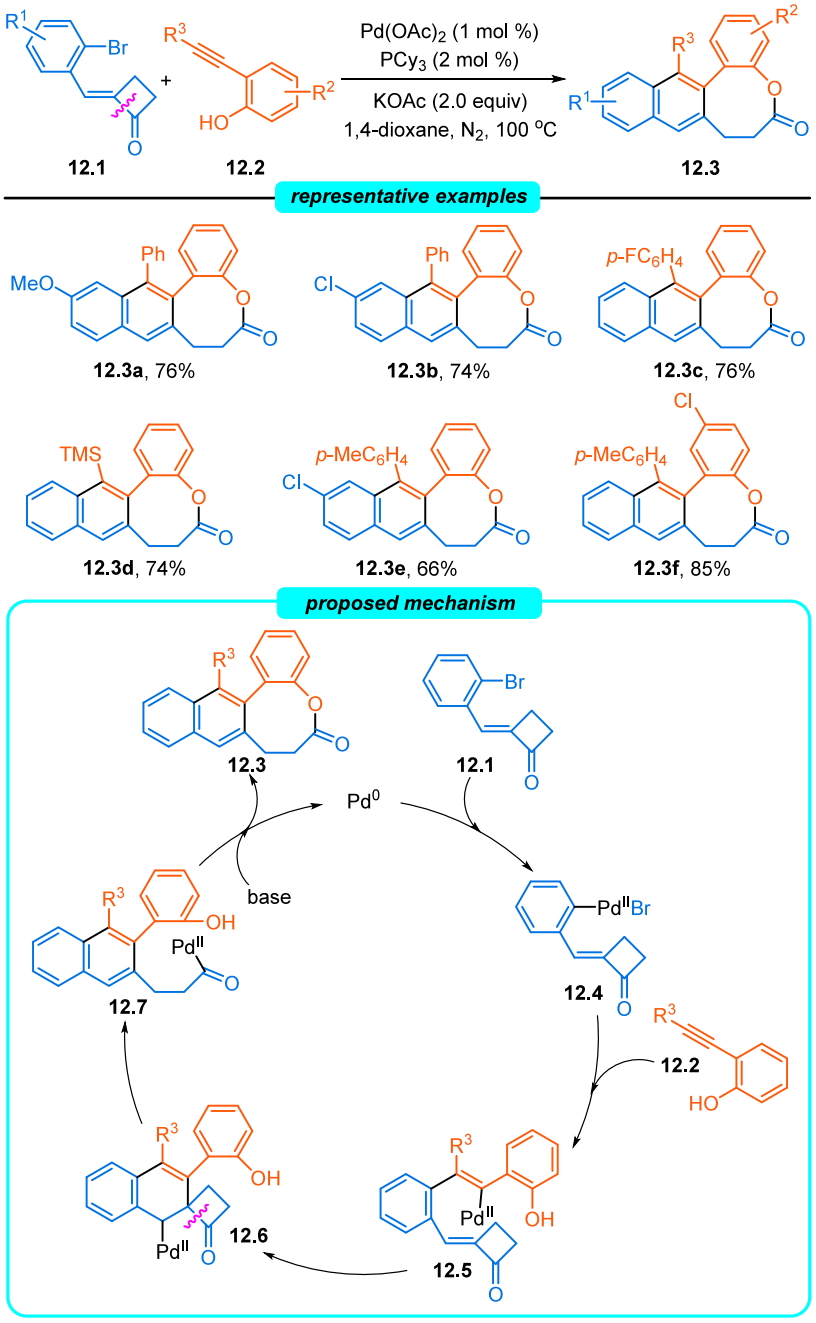
Scheme 12. Pd-Catalyzed Cascade Annulation of 2-(2-Bromobenzylidene)cyclobutanones with 2-Alkynylphenols



cyclopentane **14.3**. This strategy represents a new activation mode of the C−C bond that is distal to the alkylidene group.

Isocyanides, as highly reactive intermediates, can engage in numerous transformations for the preparation of aromatic heterocyclic compounds. In this context, the integration of an isocyanide group and an ACB scaffold into a single molecule offers new insights into reaction modalities. In 2020, the group of Wei and Shi serendipitously found that a catalytic Tl^{I} salt promoted the dimerization−cyclization of isocyanoaryl-tethered ACBs **15.1** at an elevated temperature (140 °C), delivering a series of macrocyclic molecules **15.2** incorporating both dihydroquinoline and quinoline units in moderate yields.[27] As depicted in Scheme 15, aryl-, heteroaryl-, and even alkyl-substituted ACBs proved readily amenable to this transformation. The initially proposed ionic mechanism was not supported by DFT calculations; therefore, the authors directed their efforts toward a more reasonable triplet biradical reaction mechanism, which was consistent with the calculation results. The proposed mechanism proceeds as follows: nucleophilic attack of the isocyanide carbon of one molecule on another generates 1,4-diazabutatriene intermediate **15.3**. Subsequent intramolecular nucleophilic attack of the C=C double bond of the ACB unit on the 1,4-diazabutatriene forms a zwitterion intermediate **15.4**, which undergoes an intramolecular redox process to yield a biradical intermediate **15.5**. Following excitation of **15.5** to the triplet state, radical addition to the C=C double bond of the ACB unit

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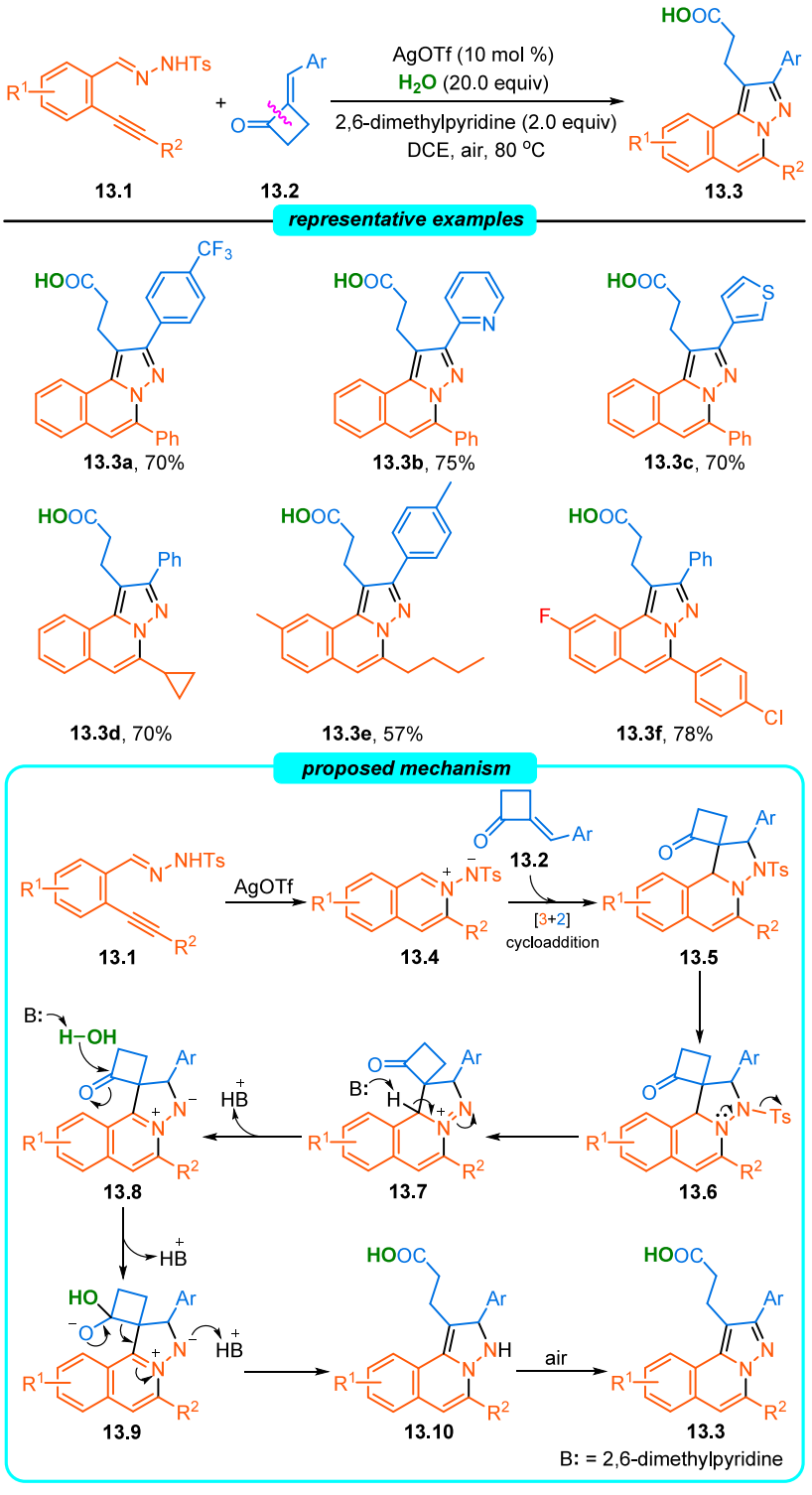
Scheme 13. Ag-Catalyzed Three-Component Tandem Reactions of 2-Alkylidenecyclobutanones



occurs to give intermediate **15.6**. Ring opening of the cyclobutane unit then takes place to provide intermediate **15.7**. Finally, radical/radical cross-coupling forges a new C−C bond, leading to the formation of macrocyclic skeleton **15.2**. TlOAc, as a Lewis acidic additive, may play a role in activating the C=C double bond via π-coordination and the isocyanide via σ-coordination. Although this transformation is fascinating and highly desirable, the major limitation of this protocol lies in the necessity of using the highly toxic thallium salt.

4. RING-EXPANSION REACTIONS OF ACBS

Emerging ring-expansion reactions of ACBs with a broad range of coupling partners have significantly propelled the rapid

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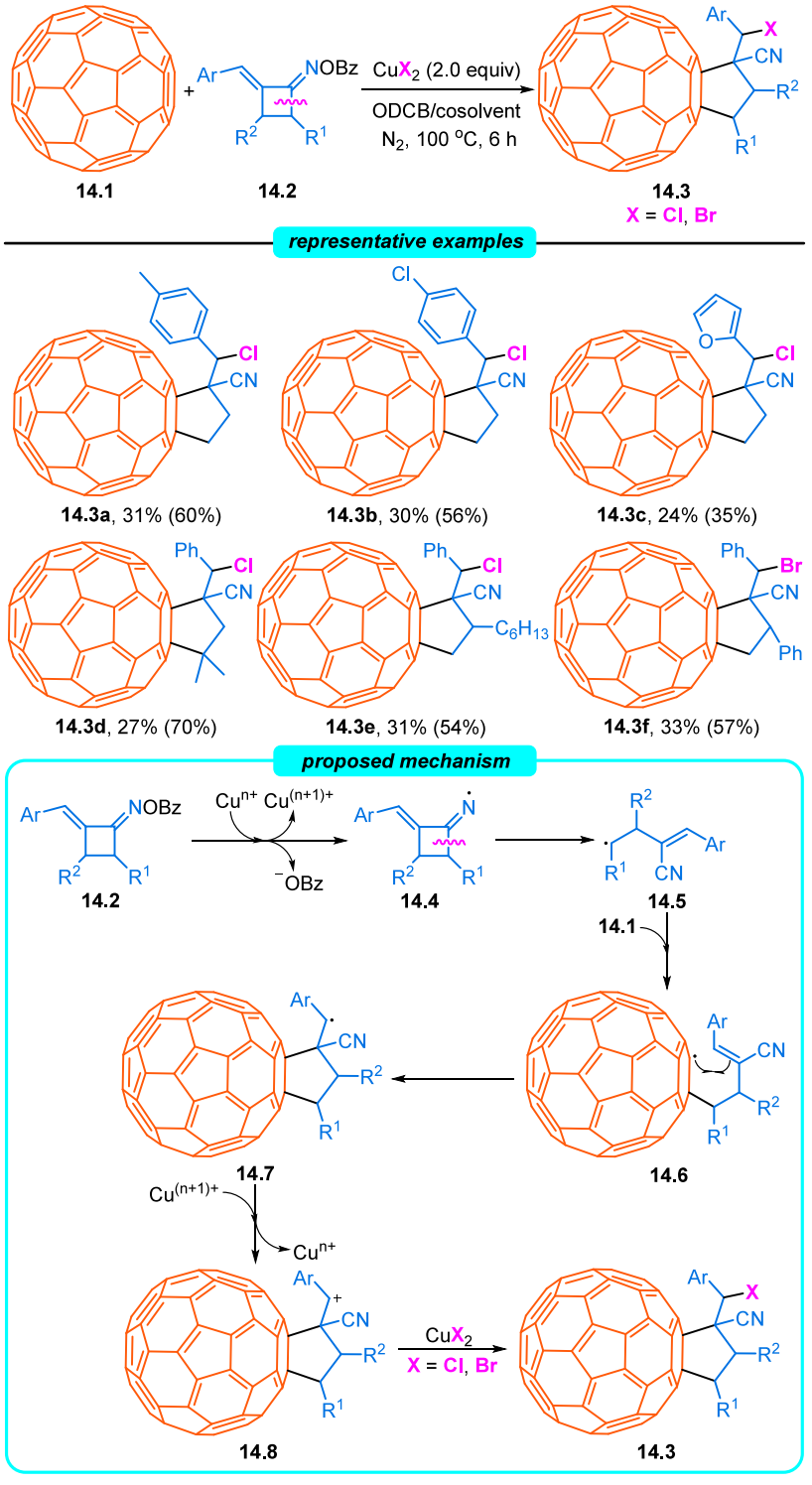
Scheme 14. Cu-Mediated Radical-Induced Ring-Opening Relay Tandem Carboannulation of [60]Fullerene with Cyclobutanone Oxime Esters



evolution of selective transformations. From a thermodynamic perspective, by taking advantage of the five-atom property of ACBs, numerous approaches mainly concentrate on the cyclization of these strained rings to more stable cyclopentanes or cyclopentanones mediated by organic or inorganic oxidants and Lewis acids. Extending this concept, incorporating an oxygen atom into the framework of 2-alkylidenecyclobutanones to access five-membered lactones can also release the ring strain and is therefore included in this section. Furthermore, under transition metal catalysis such as rhodium, ACBs coupled with other functionalities can undergo an effective intramolecular ring-expansion reaction to give rise to intriguing medium-sized

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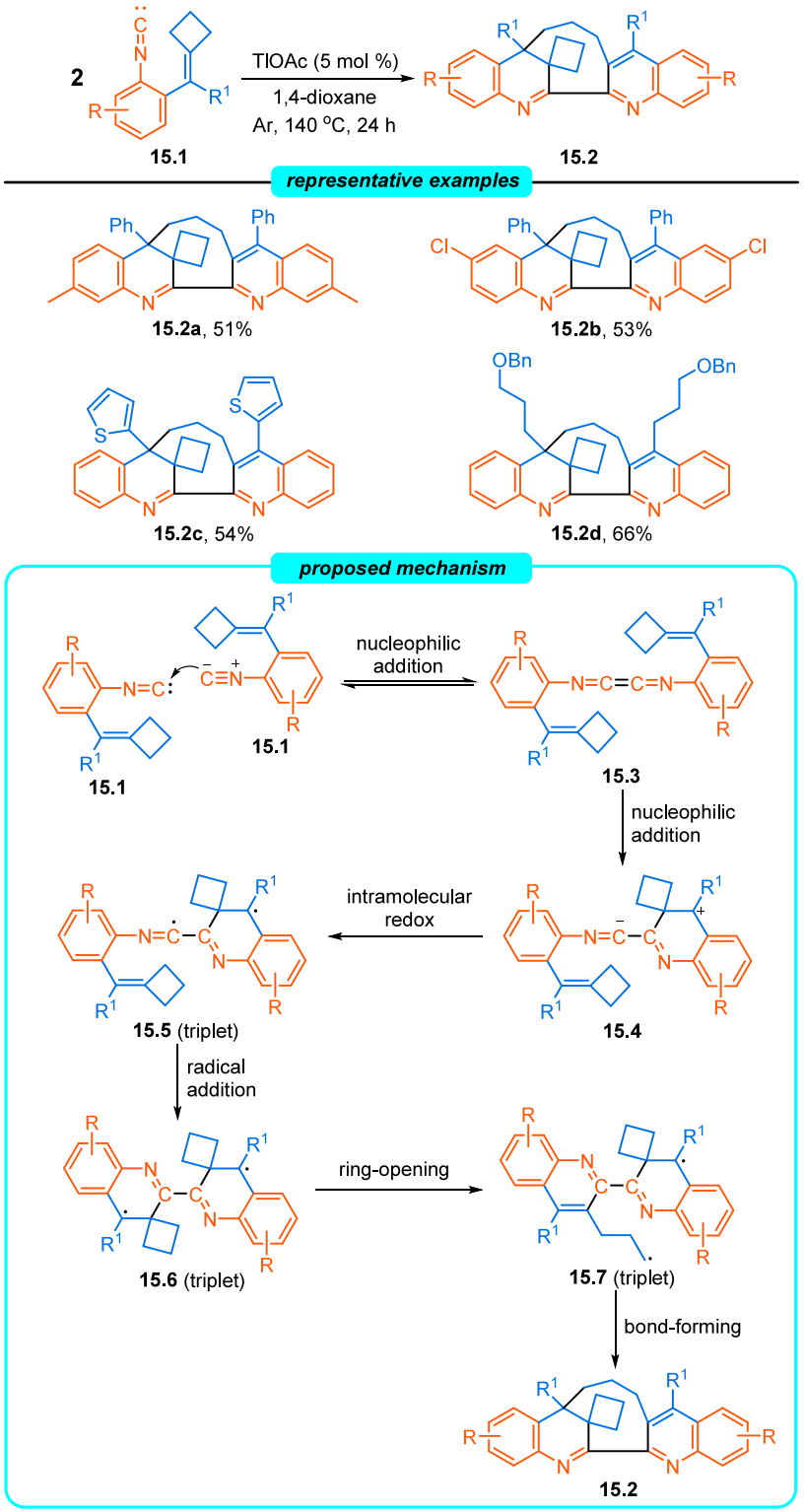
Scheme 15. Tl-Catalyzed Dimerization−Cyclization of Isocyanoaryl-Tethered ACBs



carbocycles, further highlighting the practicality of the transformations.

The ring expansion of ACBs under metal-free conditions has emerged as a promising approach for the construction of common-sized carbocyclic compounds. In 2006, following their work on nitrene equivalent-mediated ring enlargement of ACPs, Yu and co-workers also unveiled one example of the ring expansion of diphenylmethylenecyclobutane **16.2** under the same conditions, affording cyclopentylidene hydrazine **16.3** in excellent yield (Scheme 16).[28] Two plausible mechanisms were proposed. Initially, the reaction of *N*-aminophthalimide **16.1** with diacetoxyiodobenzene (DIB, $PhI(OAc)_2$) generates the

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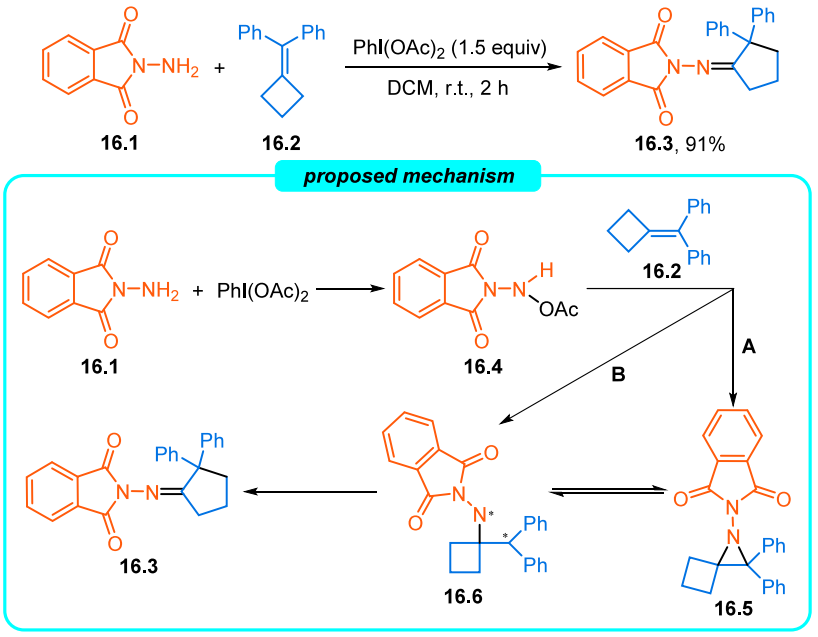
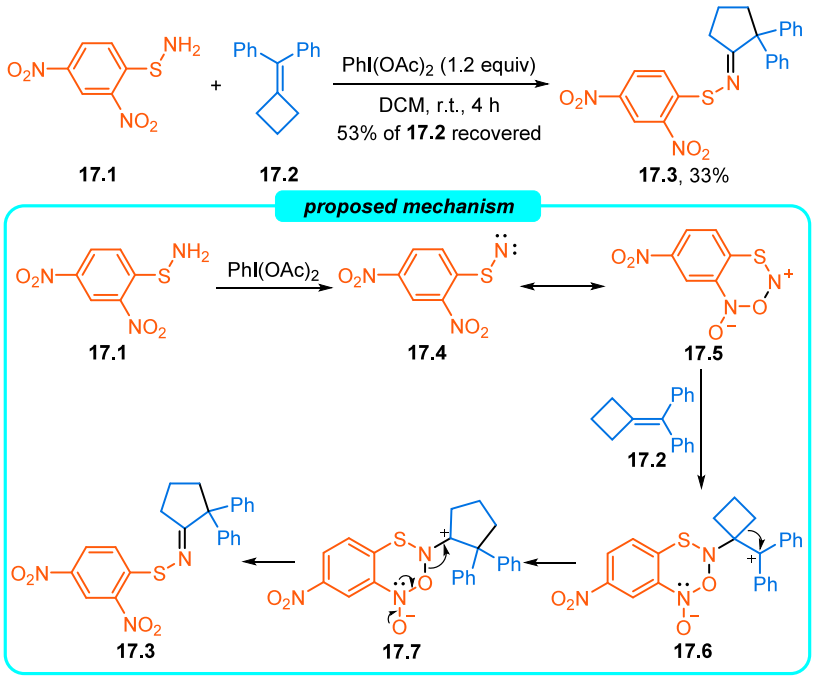
Scheme 16. Nitrene Equivalent-Mediated Ring Expansion of an ACB



Scheme 17. $PhI(OAc)_2$-Mediated Ring Enlargement of an ACB



active nitrene equivalent **16.4**, which then couples with ACB **16.2** via two distinct pathways. In pathway A, aziridine **16.5** is formed. Its subsequent rearrangement delivers cyclobutylidene hydrazine **16.3** through a diradical or ionic intermediate **16.6**. In pathway B, direct formation of intermediate **16.6** is postulated; this intermediate then undergoes a radical- or cation-initiated ring-expansion rearrangement to afford product **16.3**.

The Shi group has achieved significant progress in the field of ring-enlargement reactions of ACBs. For instance, they disclosed another example of $PhI(OAc)_2$-mediated ring expansion of an ACB **17.2** with the nitrene precursor 2,4-dinitrophenylsulfenamide **17.1** under similar reaction conditions, giving access to the (cyclopentylidene)amide product **17.3** in 33% yield, along with 53% recovery of **17.2** (Scheme 17).[29] Mechanistic studies revealed that the addition of radical scavengers such as TEMPO and BHT had no effect on the reaction outcome, suggesting that a radical pathway can be precluded. Additionally, the employment of 4-nitrophenylsulfenamide

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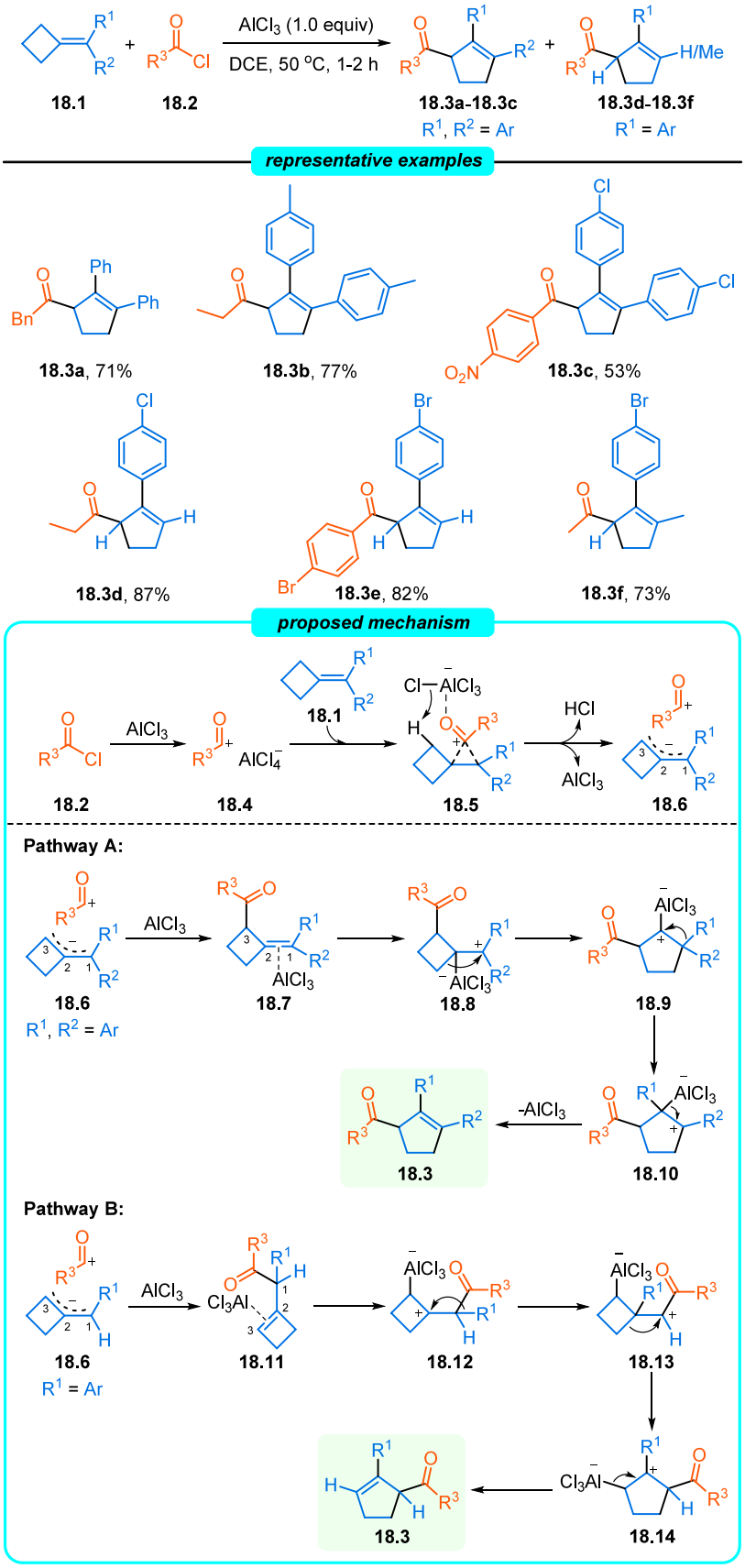
Scheme 18. $AlCl_3$-Mediated Acylation of ACBs via Ring Expansion



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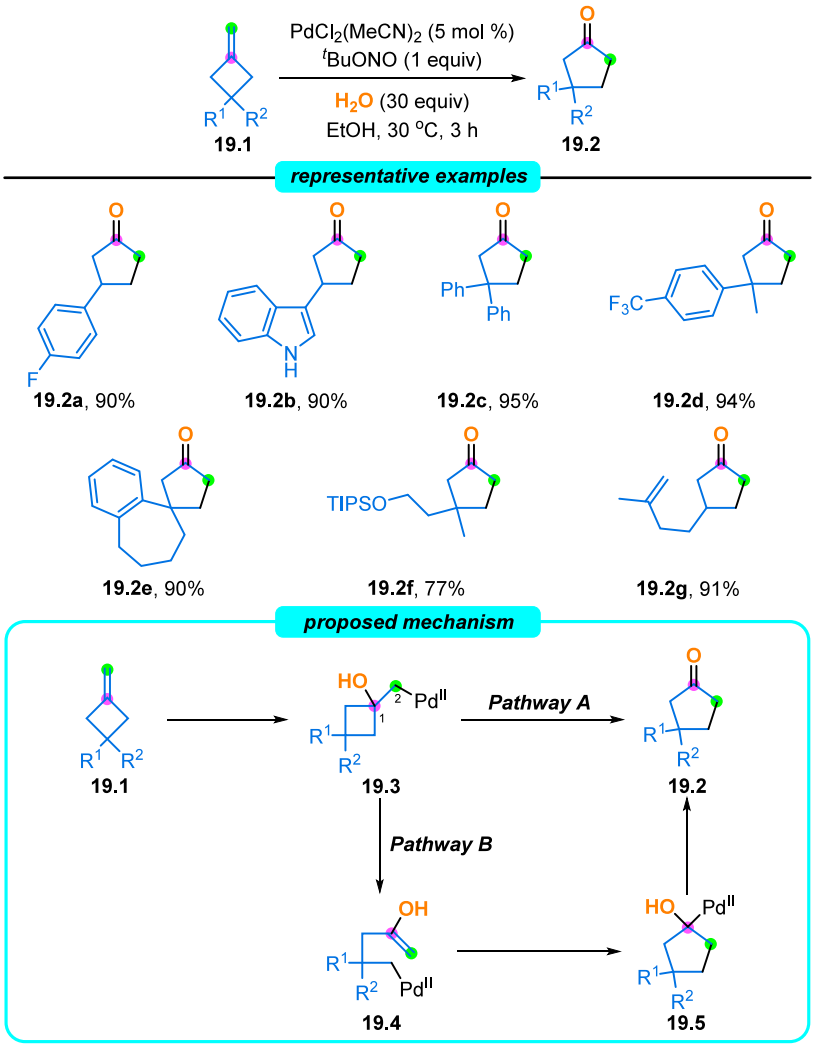
Scheme 19. Wacker Oxidation of MCBs



instead of 2,4-dinitrophenylsulfenamide did not produce the desired product, indicating the importance of the *ortho*-nitro group in initiating the reaction. Based on these control experiments, a tentative mechanism was proposed. 2,4-Dinitrophenylsulfenamide **17.1** reacts with $PhI(OAc)_2$ to form a nitrene species **17.4**, as well as its tautomer **17.5** due to neighboring group participation. Subsequent electrophilic addition of **17.5** to ACB **17.2** gives intermediate **17.6**, which undergoes a typical [1,2]-σ rearrangement to provide a cyclopentyl cation **17.7**. Finally, N−O bond cleavage furnishes the ring-expansion product **17.3**. Notably, steric hindrance between the 2,4-dinitrophenylsulfenyl group and the *gem*-diphenyl group exclusively resulted in the formation of (cyclopentylidene)amide **17.3** in the *E*-configuration.

Since the facile acylation of ACPs by Huang and co-workers in 2007,[30] the distinctive reactivity patterns of other analogous strained rings have continued to draw considerable interest. Shortly thereafter, the Shi group uncovered a Lewis acid-mediated ring-expansion acylation of ACBs **18.1** with acyl chlorides **18.2** under mild conditions, providing rapid access to a series of substituted cyclopentene derivatives (**18.3a**−**18.3f**) in moderate to high yields (Scheme 18).[31] A broad spectrum of aryl-substituted ACBs can react with acyl chlorides, driven by the release of ring strain. However, a limitation of this protocol is its incompatibility with aliphatic ACBs, in which both R^1 and R^2 are alkyl groups. Control and deuterium labeling experiments revealed two principal pathways, depending on the substitution pattern on the exocyclic double bond of ACBs. Initially, ACB **18.1** reacts with the in situ-generated acyl cation **18.4** to form intermediate **18.5**, which then undergoes elimination of an allylic proton, affording a common intermediate **18.6**. In the case of a diaryl-substituted ACB, cyclobutane acylation occurs to produce intermediate **18.7**, which upon $AlCl_3$-mediated ring enlargement with concurrent aryl transfer leads to cyclopentane cation **18.10**. Final elimination of $AlCl_3$ delivers the cyclopentene product **18.3** (pathway A). Alternatively, acylation of monoaryl-substituted ACB (R^2 = H or Me) occurs on the exocyclic carbon. The ensuing intramolecular rearrangement of the resulting intermediate **18.11** in the presence of the Lewis acid produces intermediate **18.14**, which finally eliminates $AlCl_3$ to furnish the product **18.3** (pathway B). It should be highlighted that this protocol offers a streamlined approach for accessing diverse, structurally important cyclopentene motifs.

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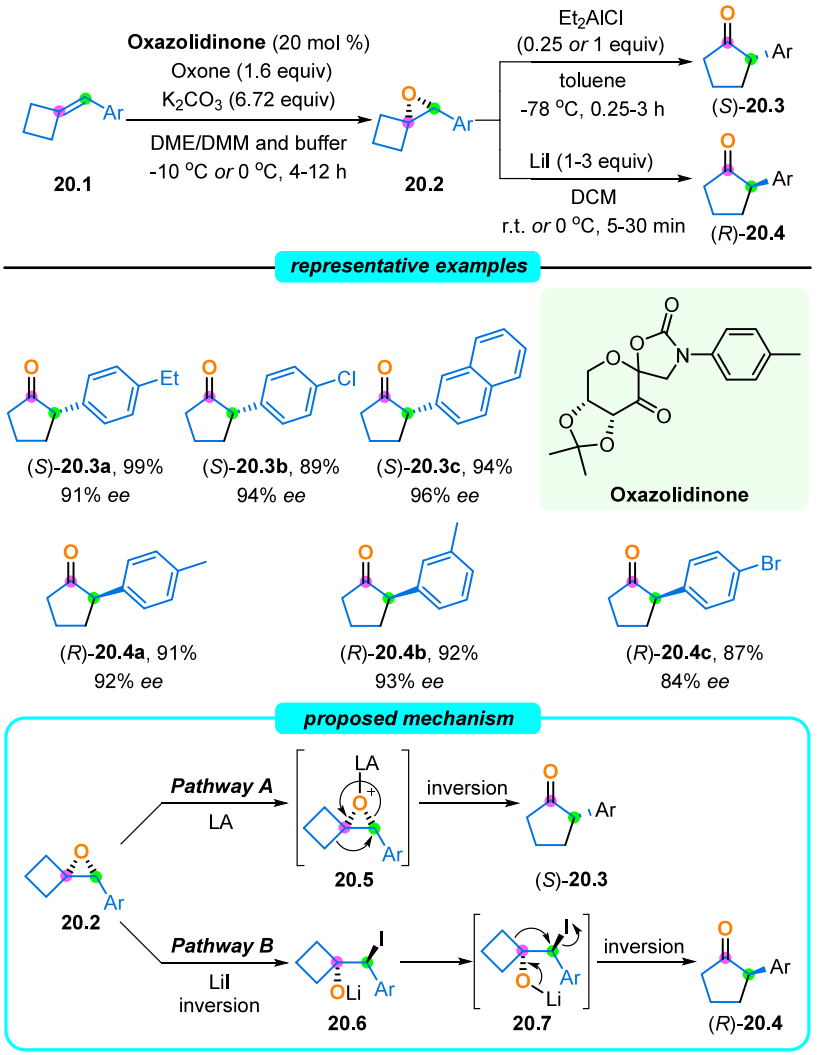
Scheme 20. Enantioselective Epoxidation of Benzylidenecyclobutanes with Subsequent Epoxide Rearrangement



MCB **19.1**, as a class of 1,1-disubstituted alkenes, was reported to undergo ketone-selective Wacker oxidation in an aqueous medium (H_2O–EtOH) through semipinacol-type rearrangement (Scheme 19).[32] Surprisingly, *tert*-butyl nitrite served as the terminal oxidant in this highly efficient ring-expansion process, not only activating the Pd^{II} catalyst through nitrite supply but also facilitating the re-oxidation of Pd^0. This catalytic oxidative protocol offers a robust platform for the synthesis of a plethora of cyclopentanones **19.2**, which features high yields, broad substrate applicability, and mild reaction conditions (30 °C for 3 h). It is noteworthy that another alkenyl group in **19.2 g** remained intact under the oxidative conditions, underscoring the high site-selectivity of this methodology. To probe the possible mechanism, an ^{18}O-labelled experiment utilizing $H_2{}^{18}O$ as a mass-sensitive tracer was conducted, which clearly supported an initial hydroxypalladation process. Moreover, the reaction outcome of the ^{13}C-labelled MCB was consistent with a 1,2-carbon shift mechanism. Accordingly, complexation and subsequent hydroxypalladation of **19.1** lead to a common intermediate **19.3**. In pathway A, a concerted 1,2-shift may take place to afford the rearranged carbonyl compound **19.2**. On the other hand, a stepwise 1,2-shift pathway cannot be ruled out, which proceeds via a sequential β-C elimination, migratory insertion, and β-H elimination (pathway B). However, an enantioselective attempt with a prochiral MCB using a pyridine–oxazoline (pyox) ligand afforded only a 63:37 enantiomeric ratio, which leaves room for further optimization of the asymmetric Wacker oxidation.

In 2006, Shi and co-workers developed an asymmetric synthesis of 2-aryl cyclopentanones ((*S*)–**20.3** and (*R*)–**20.4**) from benzylidenecyclobutanes **20.1** in two steps: enantiospecific epoxidation catalyzed by an oxazolidinone-derived ketone, followed by Lewis acid-induced rearrangement of the resulting epoxides **20.2**.[33] Interestingly, the configuration of the chiral cyclopentanones was found to be highly dependent on the type of Lewis acid employed. Specifically, Et_2AlCl-mediated epoxide rearrangement led to the (*S*)-enantiomers, whereas LiI enabled the conversion to provide the opposite enantiomers. As illustrated in Scheme 20, under the developed conditions, a variety of benzylidenecyclobutanes served as competent substrates for the asymmetric transformation, giving access to the corresponding products with high *ee* values. The authors then proposed two distinct mechanistic pathways to account for the origin of this switchable enantioselectivity. In pathway A, the epoxide

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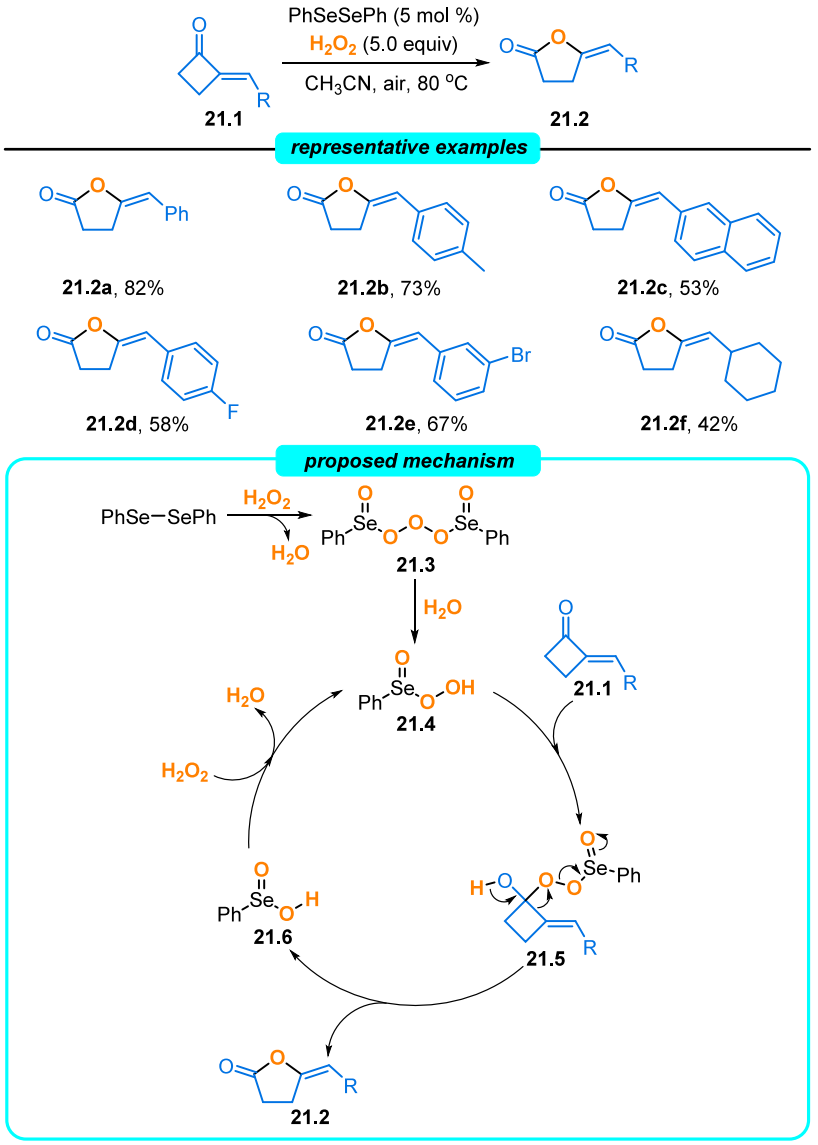
Scheme 21. $(PhSe)_2$-Catalyzed Baeyer–Villiger Oxidation of 2-Alkylidenecyclobutanones with H_2O_2



rearrangement using Et_2AlCl might proceed via a concerted process with inversion of the configuration. In pathway B, LiI likely promotes the ring opening of epoxide **20.2** to generate intermediate **20.6** with inverted configuration. Subsequent rearrangement with concomitant release of LiI furnishes (*R*)–**20.4** via a second inversion of the configuration. This two-step ring-expansion strategy offers a feasible route to optically active 2-aryl cyclopentanones that are otherwise difficult to access using traditional approaches. In a recent study by Fernández and co-workers, Shi epoxidation of ACBs bearing an axially chiral allylic alcohol moiety quantitatively provided spirocyclic compounds with the cyclobutane ring intact, albeit with low diastereoselectivity.[8j]

The stereospecific $Ca(OH)_2$-catalyzed direct aldol condensation enables the facile synthesis of highly reactive 2-alkylidenecyclobutanones, which hold significant potential for broad application in late-stage ring-expansion transformations.[17] Building upon this synthetic strategy, the incorporation of an oxygen atom into the cyclobutanone framework using either an oxidant or an acid can be recognized as another type of ring enlargement, providing expedient access to O-containing heterocycles.

In the process of investigating their reactivity profiles, Yu, Xu, and colleagues found that a diverse range of 2-alkylidenecyclobutanones **21.1** underwent Baeyer–Villiger oxidation with H_2O_2 to afford (*E*)–4-methylenebutanolides **21.2** employing the simple, inexpensive, and accessible diphenyl diselenide as the catalyst (Scheme 21).[17] This practical strategy offers an exceptional paradigm for preparing valuable lactones and exhibits a broad substrate scope of 2-alkylidenecyclobutanones **21.1** bearing a variety of functionalities. Control experiments revealed that benzeneseleninoperoxoic acid **21.4** might serve as the active oxidation catalyst. Meanwhile, ^{77}Se NMR spectroscopic analysis suggested the involvement of benzeneseleninoperoxoic anhydride **21.3** and indicated the conversion of **21.3** to **21.4** and benzeneseleninic acid **21.6** under distinct conditions. Based on the mechanistic evidence, a tentative mechanism similar to those of

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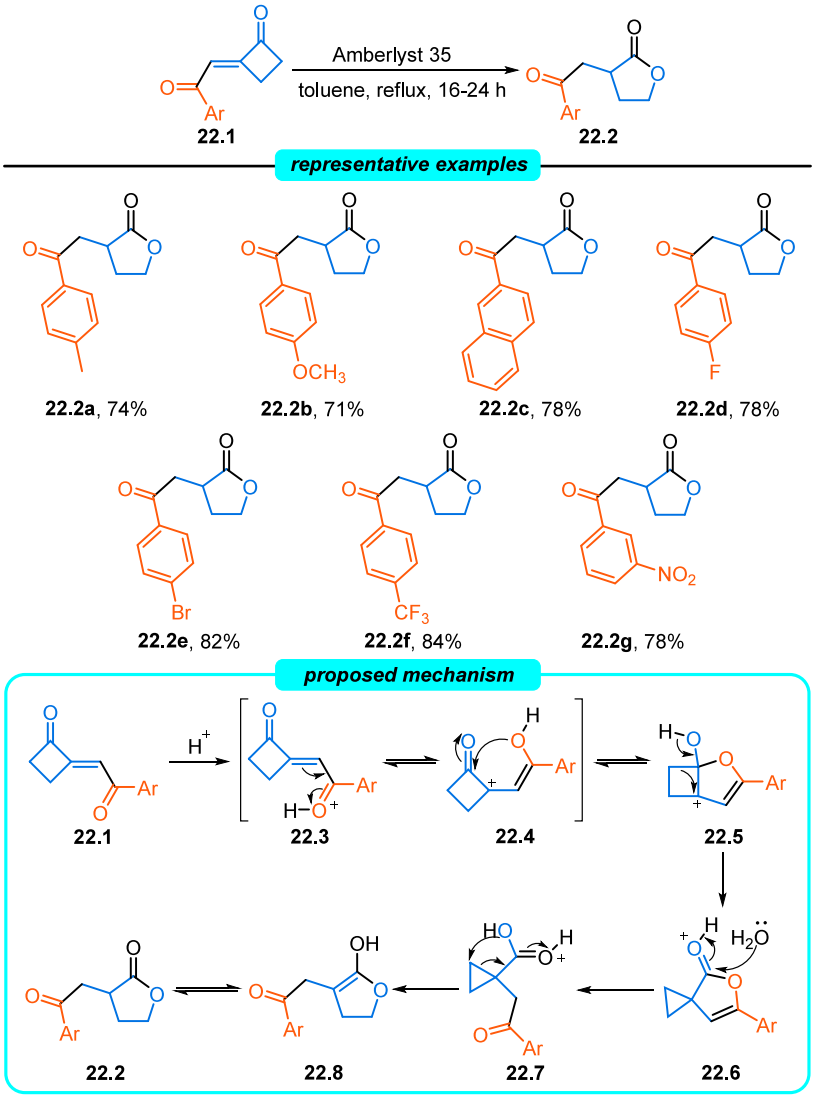
Scheme 22. Acid-Promoted Skeletal Reorganization of Pull−Pull ACBs



Baeyer−Villiger oxidation of cyclic ketones is proposed.[34] Initially, oxidation of PhSeSePh with H_2O_2 provides benzeneseleninoperoxoic anhydride **21.3**. Subsequent hydrolysis gives benzeneseleninoperoxoic acid **21.4** as the active organoselenium oxidant, which preferentially adds to the carbonyl group of **21.1** to generate intermediate **21.5**. Ultimately, a selective C−C bond cleavage owing to the activation of the exocyclic C=C double bond, followed by rearrangement, delivers the lactone **21.2** as well as benzeneseleninic acid **21.6**. The free acid can be further oxidized to regenerate **21.4** in the presence of excess H_2O_2.

In comparison with MCBs, pull−pull ACBs, namely, 2-alkylidenecyclobutanones with an electron-deficient group on the exocyclic C(sp^2) atom, are more likely to undergo strain-release-enabled reactions, leading to reorganization of the structural frameworks. In 2025, Frongia and co-workers reported a skeletal reassembly of (*E*)–2-(2-oxo-2-phenylethylidene)cyclobutan-1-ones **22.1** using Amberlyst 35 as an acid mediator to construct γ-butyrolactones **22.2** in good yields (Scheme 22).[35] Notably, this straightforward and simple strategy tolerated a diverse range of alkylidenecyclobutanones bearing electron-donating and electron-withdrawing groups on the aromatic rings and featured a step- and atom-economic manner. In control experiments, the authors found that treatment of intermediate **22.6** with Amberlyst 35 in toluene at room temperature afforded intermediate **22.7** in 91% yield. Furthermore, both intermediates (**22.6** and **22.7**) could be transformed into the desired product **22.2** under identical reaction conditions. Accordingly, a plausible mechanism consisting of a consecutive process is postulated. First, acid-promoted ring closure of **22.1** via **22.3** and **22.4** gives intermediate **22.5**, which upon further ring contraction through C−C bond cleavage generates 2(3*H*)-furanone **22.6**. Second, hydrolysis of the lactone leads to cyclopropane−carboxylic acid **22.7**. Third, an intramolecular ring-opening cyclization forms an enol intermediate **22.8**, which upon isomerization delivers the γ-butyrolactone **22.2**.

The aforementioned approaches generally result in a vast array of thermodynamically stable five-membered carbocycles or lactones. Nonetheless, ring enlargement of ACBs to medium-sized carbocycles remains an arduous task due to disfavored entropic factors along with transannular interactions.[36] Accordingly, synthetic chemists have switched their attention

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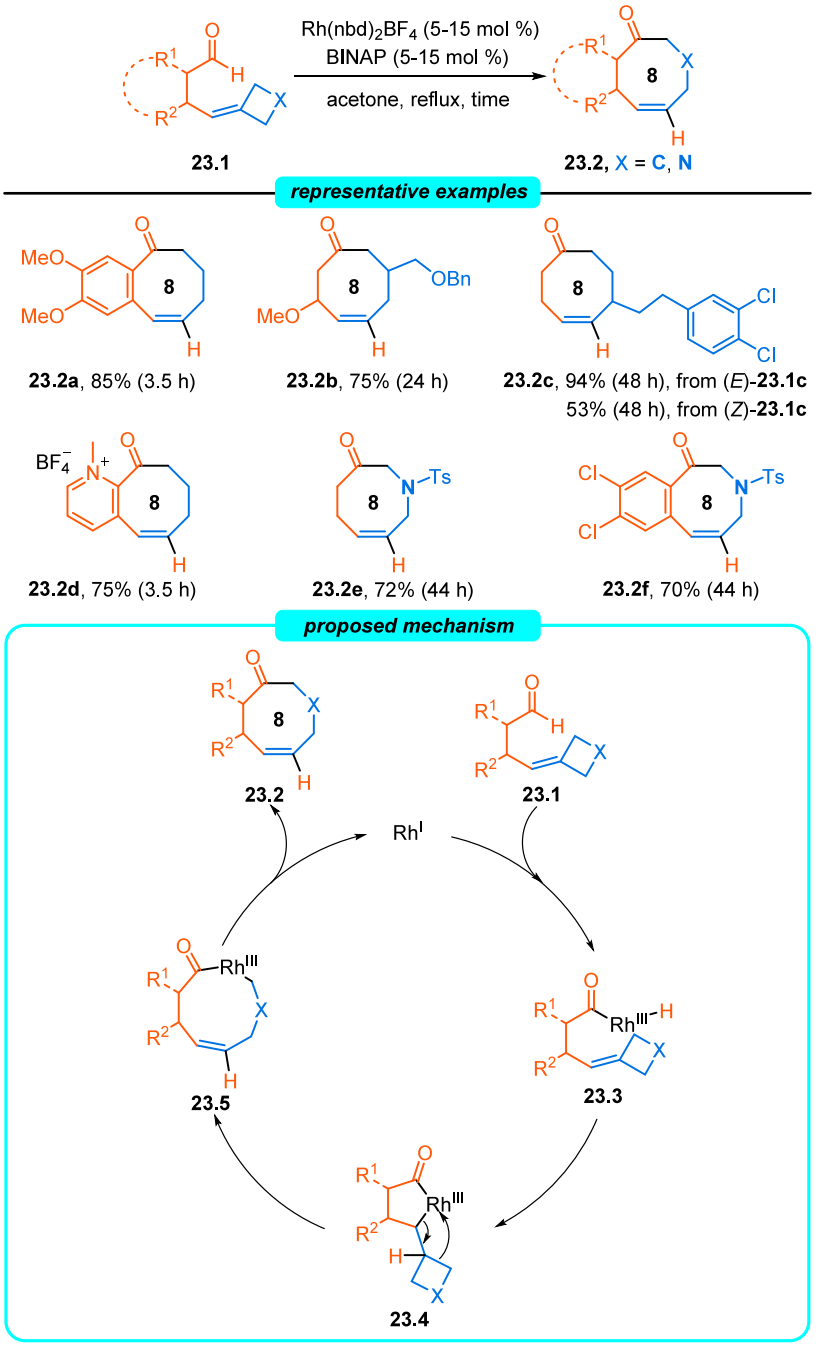
Scheme 23. Rh-Catalyzed Ring Expansion of Aldehyde-Tethered ACBs



to transition-metal-catalyzed hydroacylation of ACBs in pursuit of further breakthroughs.[37]

In 2010, Aïssa and co-workers unveiled an efficient synthesis of eight-membered carbo- and heterocyclic compounds **23.2** from aldehyde-tethered ACBs **23.1** by means of cationic Rh^{I} catalysis (Scheme 23).[38] Interestingly, both *E*- and *Z*-isomers of substrate **23.1c** were transformed into the same cyclooctenone **23.2c**. A subsequent study rationalized the hydroacylation outcome, which is presumed to proceed through three catalytic pathways involving distinct C−C bond cleavages.[39] More importantly, 3-alkylideneazetidines, as bioisosteres of ACBs, also afforded the desired products (**23.2e** and **23.2f**) in satisfactory yields, further broadening the applicability of rhodium-catalyzed intramolecular hydroacylation. According to the proposed mechanism, the classical oxidative addition of the formyl C−H bond to the Rh^{I} catalyst readily generates an acyl−Rh^{III}−H species **23.3**, which upon Markovnikov hydrometallation is converted into a putative pentarhodacycle intermediate **23.4**. Subsequent β-C elimination occurs to give a nine-membered rhodacycle intermediate **23.5**. Final reductive elimination furnishes the eight-membered carbocycle **23.2** with simultaneous regeneration of the Rh^{I} catalyst. This efficient method demonstrates the potential of ACBs in constructing medium-sized rings via C−C bond activation, thus representing

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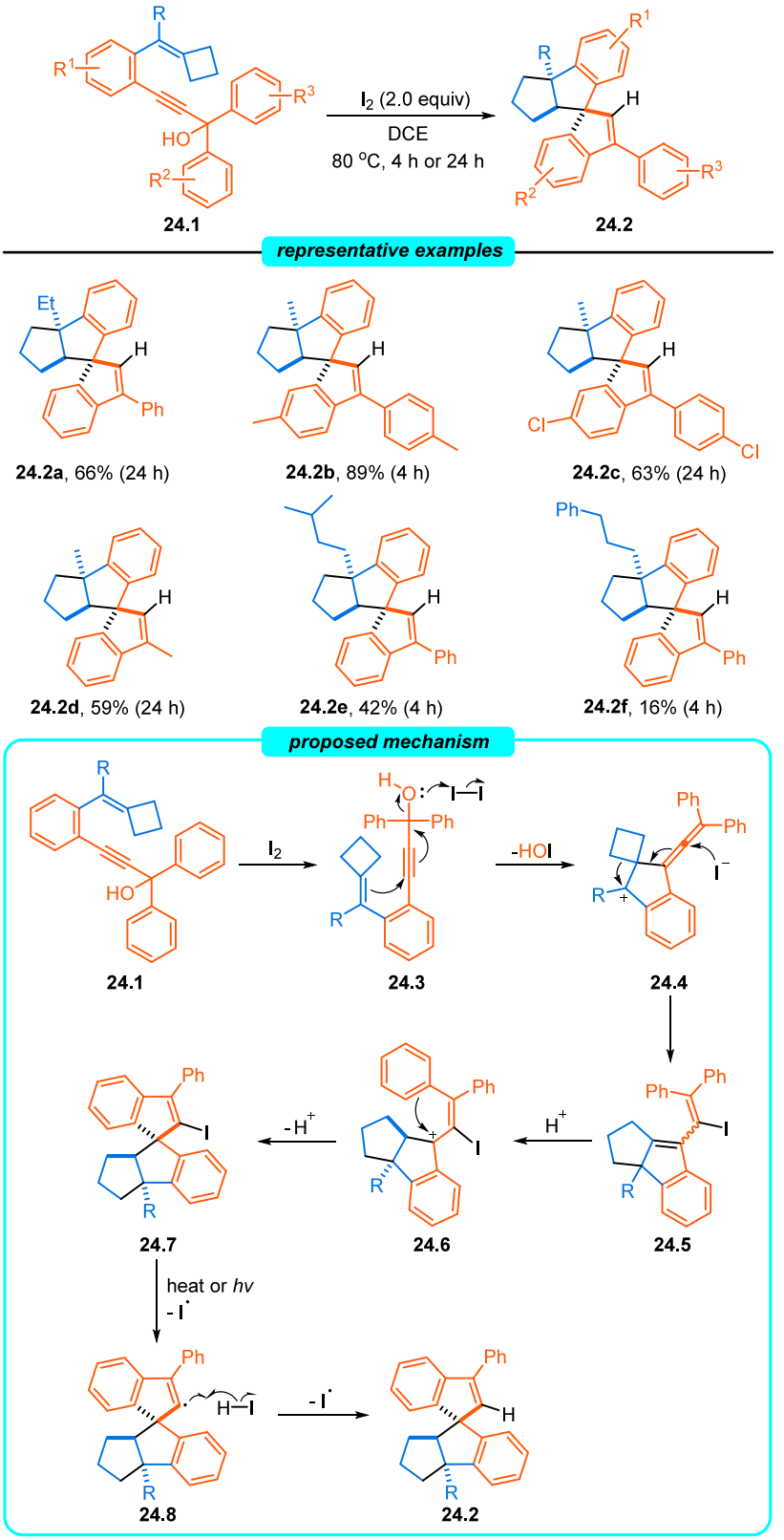
Scheme 24. Iodine-Mediated Tandem Ring Expansion and Cyclization of Propargyl Alcohol-Tethered ACBs



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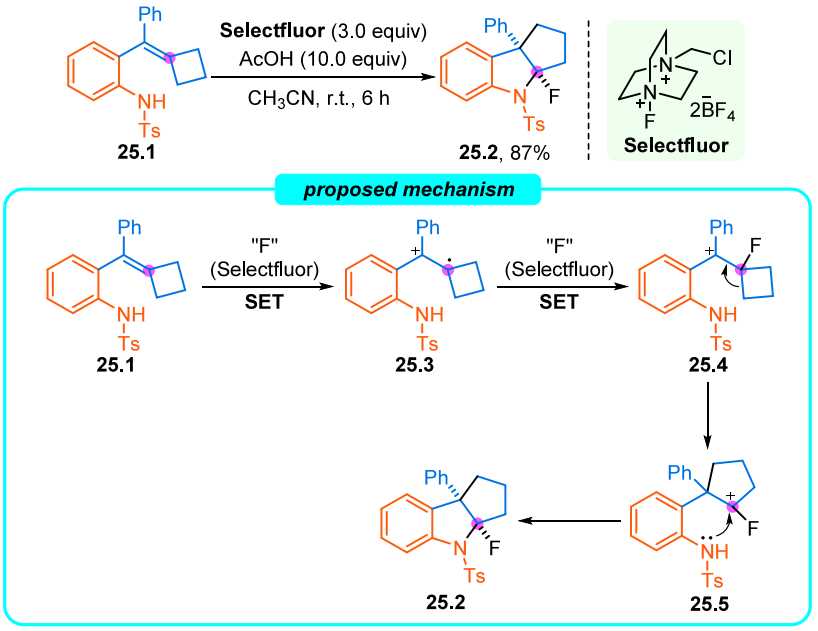
Scheme 25. *Gem*-Aminofluorination of an *Ortho*-Sulfonamide-Tethered ACB



a significant contribution to innovative synthetic methodologies.

5. CASCADE REACTIONS INVOLVING RING EXPANSION OF ACBS

Combining the ACB framework with other polar groups such as alkynyl alcohols and protected amino scaffolds is capable of initiating a variety of strategic cascade reactions, thereby providing efficient access to value-added spirocyclic and bridged compounds. In this regard, several illustrations of I_2- and Selectfluor-mediated, as well as Pd^{II}-catalyzed, transformations have been successfully established via a tandem process consisting of sequential ring expansion of ACBs and cyclization reactions. Depending on the external reagents employed, distinct mechanisms have been postulated to account for the formation of polycyclic products. These protocols have significantly broadened the application scope of ring-enlargement reactions of ACBs, impressing chemists with their inherent regioselectivity and efficiency.

The strained ACBs bearing a highly reactive functionality such as propargylic alcohol can trigger unforeseen transformations under specific reaction conditions. In continuation of their research on the advancement of novel reaction patterns of strained small-ring precursors,[40] the Shi group established an I_2-mediated sequential ring enlargement and intramolecular Friedel−Crafts-type annulation of propargyl alcohol-tethered ACBs **24.1** for the synthesis of the natural product-like spirocyclopenta[*a*]indene skeletons **24.2** (Scheme 24).[41] This cascade reaction enabled the simultaneous construction of tricyclic [6,5,5]-fused systems and spiroindene scaffolds in one pot, providing rapid access to spiropolycyclic products (**24.2a**−**24.2d**) in moderate to good yields upon introduction of a small alkyl group on ACBs. By contrast, in the case of the substrates (**24.1e** and **24.1f**) bearing a bulkier isopentyl or phenylpropyl group, the polycyclic products were obtained in low yields. Deuterium labeling experiments revealed that the protonation originated from an external proton source. Furthermore, control experiments provided unambiguous evidence that the iodinated product **24.7** was involved as the key intermediate, and subsequent hydrodeiodination might proceed through a radical pathway. Based on these investigations, a plausible mechanism for the generation of spirocyclopenta[*a*]indenes was postulated. An initial intramolecular enyne cyclization takes place through activation of the hydroxyl group of the substrate **24.1** by I_2 to form intermediate **24.4**. Subsequently, nucleophilic attack of iodide onto the allene moiety, coupled with ring expansion of the cyclobutane, leads to iodinated intermediate **24.5**, which undergoes an intramolecular Friedel−Crafts-type cyclization to give the spiropolycyclic intermediate **24.7**. Finally, homolysis of the C−I bond under heat or irradiation, followed by abstraction of a proton from HI, delivers the desired product **24.2**. Notably, the gram-scale applicability of this cascade strategy opens up intriguing avenues for the selective construction of valuable structural frameworks.

It is widely recognized that the incorporation of a fluorine atom into the scaffold of active compounds endows them with enhanced physicochemical and pharmacological profiles. However, simultaneously introducing another functional group at the geminal carbon poses a formidable task. To overcome this challenge, in 2018, the Shi group achieved an intramolecular *gem*-aminofluorination of *ortho*-sulfonamide-tethered ACB **25.1** upon treatment with 3.0 equiv of Selectfluor in the absence of any catalyst, affording a fluorinated cyclopenta[*b*]indole molecule **25.2** in high yield (Scheme 25).[42] In addition, 10 equiv of acetic acid was beneficial in promoting the reaction. The authors also found that the use of 3.0 equiv of TEMPO completely inhibited the *gem*-aminofluorination, suggesting the involvement of a radical pathway. Mechanistically, two successive SET processes proceed to form a fluorinated cyclobutylcarbinyl cation **25.4**. Subsequent Wagner−Meerwein rearrangement produces a cyclopentyl carbocation **25.5**, which upon ring closure via intramolecular nucleophilic capture by the amide group furnishes product **25.2**.

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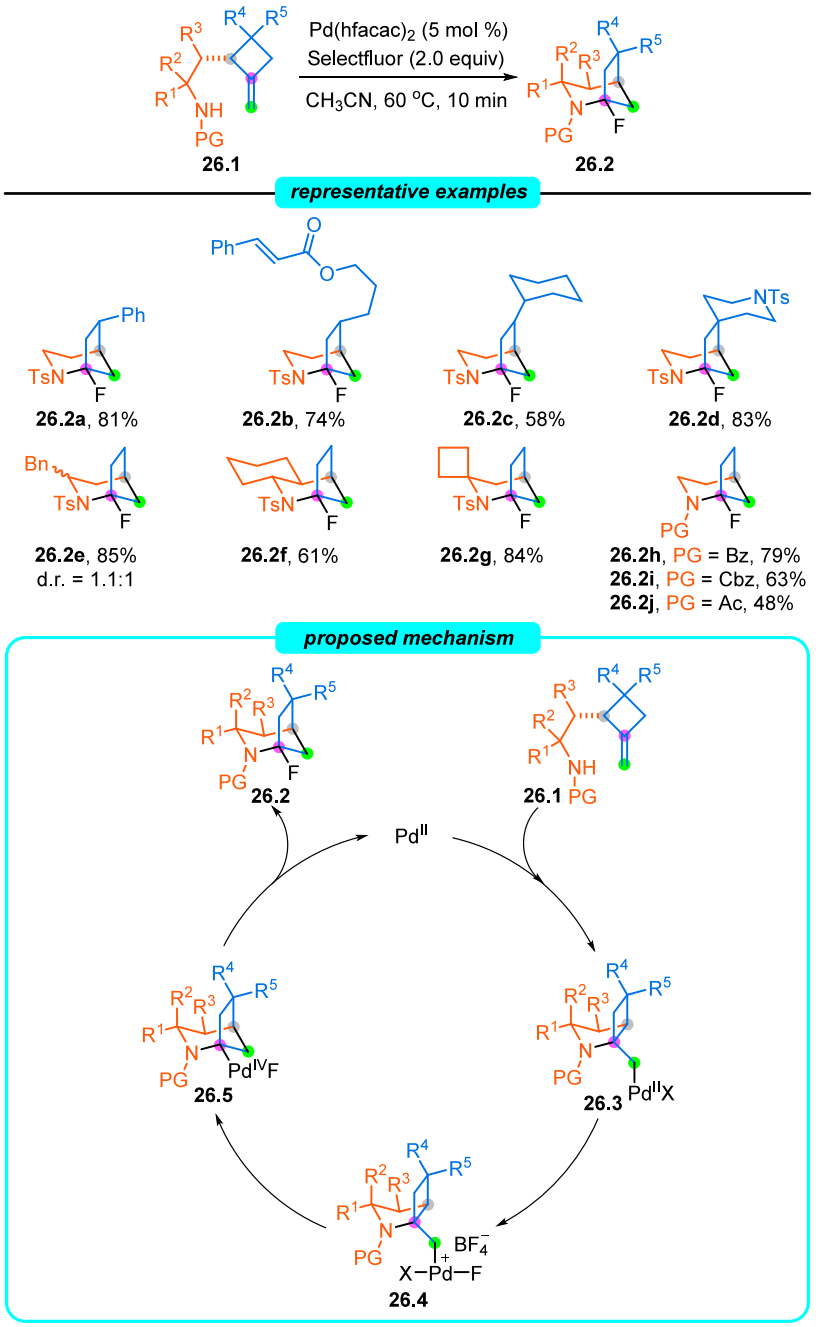
Scheme 26. Pd-Catalyzed Ring-Expanding *gem*-Amidofluorination of MCBs



In 2025, Zhu and colleagues employed the same electrophilic fluorination reagent to achieve another example of *gem*-amidofluorination of *N*-protected 2-(2-amidoethyl)−1-methylenecyclobutanes **26.1**, leading to 1-fluoro-2-azabicyclo[3.2.1]octanes **26.2** via a Pd-catalyzed ring-expanding dyotropic rearrangement (Scheme 26).[43] In this intriguing protocol, three chemical bonds, including one C−F bond, one C−N bond, and one C−C bond, are simultaneously constructed in one pot under mild conditions. In contrast to the cyclization mode observed for the intramolecular amidopalladation of diverse alkenes, which exhibited high *N*-protecting group-dependence under the Pd^{II}/Pd^{IV} catalytic cycle,[44] this transformation accommodated a wide range of readily accessible MCBs bearing distinct *N*-protecting groups (e.g., Ts, Bz, CBz, Ac). Moreover, control experiments verified the indispensable role of the palladium catalyst together with Selectfluor. The authors then meticulously conducted several mechanistic studies to elucidate the plausible pathway, which initiates with a 5-*exo*-trig amidopalladation of **26.1**. The resulting Pd^{II} intermediate **26.3** is then oxidized by Selectfluor to afford Pd^{IV} species **26.4**, which undergoes a regioselective 1,2-C/Pd^{IV} dyotropic rearrangement to form intermediate **26.5**. It is worth emphasizing that the conformational nature of the Pd^{IV} intermediate dictates the chemoselectivity of the migrating group. The final C−F bond-forming reductive elimination furnishes the bridged product **26.2** with regeneration of the active Pd^{II} catalyst. A notable advantage of

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downstream diversification of the products is the introduction of a variety of functional groups at the bridgehead carbon, thereby accessing 2-azabicyclo[3.2.1]octanes—a framework ubiquitously found in naturally occurring products.

6. CONCLUSIONS AND OUTLOOK

The foremost scientific issue in modern organic chemistry lies in the selective activation, scission, and controllable reorganization of various chemical bonds. The moderately strained ACBs stand out as particularly appealing and critical structural units in synthetic chemistry because of their ready accessibility, versatility, and distinctive reactivity patterns. Over the past two decades, a group of organic chemists has dedicated extensive efforts to ACB-participated reactions to achieve a multitude of selective transformations valuable in organic synthesis. These highly efficient systems vary from precious, earth-abundant, and rare-earth metals to readily accessible, inexpensive oxidants and acids, making possible the introduction of molecular complexity and diversity into reorganized frameworks. This perspective offers a comprehensive overview of recent advances in synthetic transformations of ACBs involving the ring opening and ring enlargement of the cyclobutane moiety with or without the assistance of the exocyclic double bond, rather than those reactions pertaining only to alkene conversion with the cyclobutane intact. We anticipate that these advancements will serve as a useful guide for researchers aiming to step into the area of strained rings. Furthermore, the mechanistic scenarios presented in most cases will not only kindle interest in transformative methods for C−C bond activation of strained rings but also prompt deeper reflection on future directions.

Despite these ingenious accomplishments in the selective transformations of ACBs, several issues remain unresolved. Fundamental challenges and emerging opportunities are highlighted as follows:

i. Although a plethora of methods for strain-releasing transformations of ACBs have been well established, these reactions are routinely restricted to the activation of the $C(sp^2)-C(sp^3)$ bond adjacent to the exocyclic double bond. Catalytic strategies for distal $C(sp^3)-C(sp^3)$ bond activation remain elusive and pose a formidable challenge with regard to selectivity control.

ii. It would be advantageous to employ ACBs without any activating groups on the cyclobutane moiety as coupling partners to exploit innovative and efficient transformations while avoiding the tedious procedures involved in the removal of these groups.

iii. Photoinduced, electrocatalytic, and enzymatic ring-opening and ring-expanding reactions of ACBs represent energy-efficient and environmentally sustainable strategies, but they are still in their infancy.

iv. Novel catalytic systems for the enantiospecific, strain-release-enabled transformations of ACBs by means of chiral catalysts or ligands have yet to be adequately developed and are highly desirable.

The advent of state-of-the-art synthetic strategies will bring about new breakthroughs in addressing the aforementioned constraints on ACB transformations by a judicious synthetic setting, with theoretical calculations deepening our understanding of the reaction mechanism. Such advances are expected not only to expand the synthetic utility of ACBs but also set the stage for the design of more complex molecular architectures with high efficiency and selectivity. In the near future, we will also present our new findings on the selective functionalization of ACBs.

AUTHOR INFORMATION

Corresponding Author

Hong-Shuang Li – *State Key Laboratory of Advanced Drug Delivery and Release Systems, School of Pharmaceutical Sciences & Institute of Materia Medica, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan 250117, P. R. China;* orcid.org/0000-0002-1740-8876; Email: hsli@sdfmu.edu.cn

Authors

Yu Teng – *State Key Laboratory of Advanced Drug Delivery and Release Systems, School of Pharmaceutical Sciences & Institute of Materia Medica, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan 250117, P. R. China*

Meng-Qiang Cai – *State Key Laboratory of Advanced Drug Delivery and Release Systems, School of Pharmaceutical Sciences & Institute of Materia Medica, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan 250117, P. R. China*

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acscatal.6c03464

Author Contributions

[§]Y.T. and M.-Q.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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